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Cellulose-Based Superabsorbent Hydrogels

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With 543 Figures and 90 Tables

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In memory of my beloved parents
Abul Hossain Mondal and Mazeda Begum
and
to my family
Mita, Maria, and Rafia

Preface

Hydrogels are a particular class of macromolecular gels obtained by the chemical stabilization of hydrophilic polymers in a three-dimensional network, in which the dispersed phase is water. They are able to absorb and retain large volumes of water from any aqueous solution or biological fluid and release it in response to specific environmental stimuli. The applications of hydrogel technologies are being widely used as absorbent cores in hygiene products (such as baby diapers, personal healthcare products, etc.), for drug delivery, in tissue engineering, in pharmaceutical and biomedical products, as water retainers, and as carriers of agrochemicals (such as fertilizers, insecticides, etc.) in agriculture and biotechnology. The flexibility and high water content properties of hydrogels are similar to those of natural tissue, making them extremely suitable for biomaterial applications. The rapidly growing business has motivated multinational companies to develop new hydrogel technologies, with a focus on consumer expectations.

However, most of the superabsorbent hydrogels that are currently on the market are acrylate-based products. Hence, they are not biodegradable and biocompatible, and, most importantly, some concerns exist about their toxicity. This limits their application to products related to human use or consumption. As a result, the renewed attention of institutions and public to the environment has led manufacturers to consider the development of nontoxic, biodegradable, and biocompatible superabsorbent hydrogels.

Cellulose is the most abundant, relatively simple, easily accessible, and cheap biomolecule in nature. In addition, the fabrication of cellulose-based superabsorbent hydrogels is cost effective and environment friendly. Cellulose is a promising natural polymer material because of its hydrophilicity, renewability, biodegradability, biocompatibility, and nontoxicity. Thus, cellulose-based hydrogels, as well as other natural polymer-based hydrogels (or bio-based hydrogels), can have the abovementioned favorable properties.

This book presents the first comprehensive reference concerned exclusively with this topic. The book provides easy access to the subject, both for those who are just starting to work in the field and for experienced academic and industrial professionals. It presents a broad survey, with insight, of synthesis, hydrogel modification, mechanism of formation, characterization, behavior, structure and functions relationships, and applications of cellulose-based superabsorbent hydrogels as well as other

bio-based hydrogels. The potential applications of cellulose-based hydrogels are in the fields of drug delivery, pharmaceuticals and biomedicine/biomaterials, tissue engineering, wound dressing, food packaging, water purification, agriculture, horticulture, etc. The book thus covers all these fields. The references in each chapter of the book provide a basis for deeper investigation of the recent advances in the field.

This book deals with cellulose-based hydrogel functioning materials and other bio-based materials. Each chapter explains the current status of research and technology in the study of synthesis routes or design concepts, methods and fabrication strategies, characterization and applications of cellulose-based hydrogels, as well as future prospects for research in the subject area. The book is intended mainly for polymer chemists and experts in materials science. Other potential readers are industrial scientists and engineers, agricultural engineers, pharmaceutical and biomedical scientists, and biotechnologists engaged in research and development on absorbency, absorbent products, and superabsorbent hydrogels. This book can also be helpful to graduate and undergraduate students.

Cellulose-Based Superabsorbent Hydrogels is a comprehensive major reference book. It is divided into two volumes that are organized into five parts:

Part I. Fundamentals of Cellulose, Superabsorbents, and Hydrogels
Part II. Synthesis of Cellulose-Based Hydrogels
Part III. Characterization Tools and Techniques of Hydrogels
Part IV. Applications of Biocompatible Hydrogels
Part V. Other Bio-Based Hydrogels and Their Applications

There are altogether 60 chapters in these five parts.

Part I, Fundamentals of Cellulose, Superabsorbents, and Hydrogels, concentrates on the fundamental aspects and the theoretical basis of different types of common and smart hydrogels. This part covers synthesis, structure formation mechanism, functions, and performance of both synthetic- and cellulose-based superabsorbents. It also covers stimuli-responsive, enzyme-responsive, and multifunctional hydrogels. This part discusses some of the important specific features of hydrogels that should be considered and understood in synthesis for target applications, such as technological feasibility of cellulose-based hydrogels with respect to environmental sustainability, physicochemical properties in structure–property relationships, mechanistic roles of cellulose and cellulose derivatives in cellulose-based absorbents, absorption and gelation mechanisms for superabsorbency, and the advantages of biorenewable hydrogels over synthetic hydrogels. The up-to-date research advances, future research scope, and diverse applications of cellulose-based hydrogels in pharmaceuticals, biomedicine, and agriculture are overviewed in this part.

Part II, Synthesis of Cellulose-Based Hydrogels, summarizes major design concepts, synthesis routes, preparation and modification methods, and fabrication of different types of cellulose-based hydrogels. Cellulose is very susceptible to various organic and inorganic chemicals, due to which many cellulose derivatives, as well as hydrogels, with either hydrophilic or hydrophobic characteristics, are

possible. The production methods of superabsorbent hydrogels and aerogels, composite and nanocomposite hydrogels, surface-functionalized hydrogels, and conductive and smart hydrogels from cellulosic materials by various polymerization reaction methods and irradiation techniques are described in this part. To develop 3D-cross-linked cellulose-based hydrogels, polymerization reaction engineering as well as its kinetics and mechanisms are also highlighted.

Part III, Characterization Tools and Techniques of Hydrogels, covers the characterization and analysis of cellulose-based hydrogels using different physicochemical and instrumental techniques. Physicochemical, morphological, structural, thermal, and the relevant instrumental analyses are discussed in this part to elucidate the three-dimensional network structure of cellulose-based hydrogels. Their structural, functional, surface, and interfacial absorption and swelling mechanisms are also described. Experimental methods to measure the elastic modulus of hydrogels, depending on their measurement scale, whether macroscale, mesoscale, or microscale, are also reviewed. The designed hydrogels can be characterized by physicochemical and sol-gel analyses and instrumental analyses, such as Fourier-transform infrared spectroscopy (FTIR), nuclear magnetic resonance (NMR) spectroscopy, X-ray diffraction (XRD), scanning electron microscopy (SEM), transmission electron microscopy (TEM), atomic force microscopy (AFM), polarized optical microscopy (POM), thermogravimetric analysis (TGA), differential scanning calorimetry (DSC), dynamic mechanical analysis (DMA), and thermomechanical analysis (TMA), to investigate and elucidate the desired product structure, functions, and application performance.

Part IV, Applications of Biocompatible Hydrogels, covers the diverse range and uses of biodegradable and biocompatible cellulose-based hydrogels. This part discusses different important applications which are essential and sustainable for human beings, other living things, and the environment. Each chapter describes specific types of applications in detail. The superabsorbency, permeability, flexibility, and high water content properties of hydrogels give this class of materials an amazing array of uses. These uses range from antimicrobial, antifungal, nontoxic, hygiene, biodegradable wound dressing, personal care, and food packaging products to products used in the fields of drug delivery, pharmaceuticals and biomedicine, tissue engineering, and regenerative medicine. These materials are also widely used for a range of smart applications, such as stimuli-response materials, oil contaminant removal, smart corrosion inhibitors, delivery of agrochemicals (pesticides, fertilizers, etc.), water treatment, and water retention in desert and arid areas. All these applications are vividly described in detail with tables, figures, and illustrations in this part.

Part V, Other Bio-Based Hydrogels and Their Applications, summarizes synthesis, design concepts, mechanism of formation, fabrication, characterization, performance, and applications of important bio-based hydrogels. The biodegradable bio-based hydrogels are derived from polysaccharides, carbohydrates, chitosan, protein, gelatin, collagen, and silk. Two chapters in this part differ slightly from the others: ▶ Chapter 46 summarizes the applications of synthetic hydrogels as absorbing materials for the removal of pollutants, dyes, heavy metals, and

radioactive elements as well as for controlled and sustained release of agrochemicals and explains their impacts on health and the environment. ▶ Chapter 52 highlights the importance of PLA-based hydrogels in biomedical applications, with a significant focus on scaffolds for the treatment of damaged tissues.

All the authors who were invited to write chapters in this book have many years of experience in hydrogel research, and their knowledge is succinctly condensed in this volume. Each chapter is an authoritative treatise on its specific topic and can be read independently. Vivid schematics and illustrations in each chapter, as well as throughout the book, enhance the accessibility of the theory and technologies described therein. All chapters of this book were reviewed by at least one reviewer, revised by the authors according to reviewers' comments, and then edited by the editor.

The editor would like to express his gratitude to all prominent academics and professionals for their excellent contributions to this book and to the reviewers for their efforts and valuable comments. He gratefully acknowledges Springer International Publishing AG, Switzerland, for allowing him the opportunity to participate in this publication and also expresses his sincere thanks to Lydia Mueller and Dr. Sylvia Blago, Support Staff for Major Reference Works of Springer International Publishing AG, for their support and helpful suggestions along the way.

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The editor hopes that the book will serve as a useful reference to students, researchers, academics, and industrialists in the field of bio-based hydrogel research.

Any constructive suggestions and comments are therefore welcome for future revisions and corrections.

Department of Applied Chemistry and Chemical Engineering
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November 2018

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Part I

Fundamentals of Cellulose, Superabsorbents, and Hydrogels

Cellulosic Hydrogels: A Greener Solution of Sustainability

1

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Contents

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Abstract

Hydrogels are insoluble three-dimensional cross-linked polymeric network that swells in presence of water and other fluids. They can hold plenty of water compared to its own mass. The absence of dissolution attraction toward water is due to hydrophilic nature of the polymeric chain. Hydrophilicity arises because of holding hydrophilic functional groups in the chain. Highest portion of the world production of hydrogels is petrochemical based which is neither renewable nor biocompatible. In spite of some drawbacks like nondegradability, synthetic hydrogels are superior to natural one in water absorbency, diversification in chemicals, and longer service life. Taking into consideration sustainability factor, scientists are interested in preparation of hydrogels from renewable cellulosic sources. As cellulose possesses intrinsic nature of degradability, biocompatibility, and nontoxicity, also available in nature, and some cellulose derivatives show smart behavior, cellulose-based hydrogels can be an alternative to synthetic petrochemical-derived hydrogels. Numerous research articles concerning the synthesis and utilization of hydrogels in different fields have been published, and still restless labor is giving for the betterment of the product quality. It is a crying need to make available and adequate information on synthesis and characterization of cellulosic hydrogels for individual researchers. For this the specific aim of this paper is to accumulate some crucial information which will cover synthesis, detailed classification, characterization, and technological feasibility of application about hydrogels of renewable source. As of consequence, the research on hydrogel concerning current environmental issues will reach to its target of making the greener solution of sustainability. In addition, recent trend of hydrogel research is also discussed in this review.

Keywords

Cellulose · Cellulosic hydrogel · Cellulose derivatives · Hydrophilic · Renewable · Biocompatible · Sustainability

1 Introduction

Hydrogels are gel-like materials with hydrophilic functional groups in polymeric chain and capable of holding large volume of hydrofluids compared to its own mass. It can also be defined as hydrogels are water-absorbing natural or synthetic polymeric substance which swells in water and retain a significant amount of water within the structure without dissolving in water [1–3]. Hydrogels attract water due to polar functional groups on the skeleton of macromolecule and inhibit dissolving due to cross-linking. Both types of cross-linking, chemical or physical, can exist in the macromolecular chain. After absorption, generally hydrogels swell until the thermodynamic force of swelling is totally counterbalanced by the elastic, retroactive force exerted by the cross-links. The volume of water taken up by macromolecule depends on the structure of the polymer network itself and on the environmental conditions, such as the temperature, pH, and ionic strength of the water solution in contact with the polymer [4, 5]. The most important variable that affects the diffusive, mechanical, optical, acoustic, and surface properties of the hydrogel for given environmental conditions is the volume or mass swelling ratio of the hydrogel.

Hydrogels are of mainly two categories based on their natural or synthetic origin: biopolymer-based and synthetic. Hydrogels prepared at the early stage are non-biodegradable and originated from nonrenewable petroleum based. Among various biopolymers, cellulose is largely available in nature and shows hydrophilic nature and good mechanical properties because of enormous hydroxyl groups. The mechanical strength and its insolubility in water and in the major part of solvents depend mainly on the complex system of hydrogen bonds between hydroxyl groups. Due to plentiful hydrophilic functional groups, it gives possibility to cellulose as promising material for hydrogel preparation. Generally natural polymers, especially polysaccharide-based hydrogels, find application in many fields (agriculture, tissue engineering, drug delivery, biosensors, etc.) and make scientists interested about the matter due to some unique qualities like eco-friendly, renewable, and low cost. Among various polysaccharides, few have been investigated on hydrogel formulations, such as chitosan [6, 7], starch [8, 9], cellulose [9], alginate [10], carrageenan [11], and gellan gum [12].

Manufacture of hydrogels from cellulose generally is accomplished in two steps [4, 6, 7, 11], (i) dissolving of cellulose fibers or powder and (ii) cross-linking (chemical and/or physical) of the chains, in order to obtain a three-dimensional network of hydrophilic polymer chains, which is able to absorb and retain a significant amount of water. It is also reported that cellulose-based hydrogels were prepared and used as a novel porous bioabsorbent by graft copolymerization for absorption of heavy metal ions from aqueous solutions. Therefore, the diversified application of cellulose-based hydrogels is flourishing gradually. After the invention of first hydrogels by Otto Wichterle in the 1950s [13], from then scientists are trying to improve the qualities and to make novel superabsorbent which will fulfill the required expectations. The modern application of cellulose and its derivatives

includes environment-friendly and economic nonaqueous gel polymer electrolytes for lithium and sodium ion batteries [14–16], aqueous electric double-layer capacitors, dye-sensitized solar cells [17], and starting materials for proton-exchange membranes (PEMs) in PEM fuel cells (FCs) [18].

It is obvious that cellulose and cellulose derivatives will not replace petroleum-based superabsorbent materials completely, but incorporation or use of the materials will bring some good qualities in hydrogels like biodegradability, biocompatibility, nontoxicity, cost-effectiveness, etc. As we know cellulose is the main constituent of plant and at the end use it decomposes. Moreover, the cellulose-based hydrogels are reusable, and processes involve less wastage of chemicals and not releasing greenhouse gases to environment, so the process can be mentioned as greener technology.

The aim of the review paper is discussion from cellulose-based published literature of hydrogels and focuses the types, use, and world consumption scenario, synthesis, controlling factors of reaction, etc. of cellulose-based hydrogels which will be an informative and fruitful tool to solve the sustainability problem. After discussing characterization techniques, some well-established and innovative applications of synthetic and cellulose and its derivatives hydrogels both are also discussed, with some suggestions for future developments.

2 History and Market Size of Hydrogels

In 1938, the first water absorbent was synthesized by thermal polymerization of acrylic acid and divinyl benzene in aqueous medium [5]. Later in 1950, Otto Wichterle [13] synthesized first generation hydrogels which were based on poly (hydroxyethylmethacrylate) (PHEMA) and used in contact lenses. Though the swelling capacity of hydrogels from same type of monomers was only 40–50%, it was a revolution in ophthalmology [19].

The first commercial synthetic-type superabsorbent polymer (SAP) hydrogel was starch-graft-polyacrylonitrile (SPAN), and its hydrolyzed product (HSPAN) was developed in the 1970s at the Northern Regional Research Laboratory of the US Department of Agriculture [20]. The product did not get commercial success due to expenses and inherent structural disadvantage (lack of sufficient gel strength) of this product. Japan started their first commercial production of hydrogel in 1978 for use in feminine napkins and later in 1980 Germany and France started using in baby diaper. Japan started manufacturing diaper in 1983 with 4–5 g SAP, hydrogel in every single piece of diaper. Within very short time, other countries in Asia, USA, and Europe also started manufacturing diaper with hydrogels. Practically SAP, hydrogels brought a drastic change in the concept of diaper item to replace fluff cellulosic materials. Finally, the diaper became thinner by the use of hydrogels. Actually within one decade, huge development occurred in personal health-care product.

From an online data analysis, it has been found that the worldwide hydrogel production and consumption are increasing. In this case, China is the biggest market

in the Asia-Pacific region, and the USA is the largest end user and producer of SAP in the North American region. Both countries are the largest consumers in their respective regions and are expected to compete with each other to dominate the market by 2020, with advanced SAP materials for end users. Current market size of superabsorbent polymer was estimated at 2.07 million tons in 2014 and is likely to exceed 3.1 million tons by 2023 growing with an expected compound annual growth rate (CAGR) of over 5.5%. It has also estimated that the worth of global market value of SAP will reach USD 7.96 billion by 2020.

Renewable raw materials such as starch, cellulose, natural gums, and chitin have been used in the manufacture of biobased SAP. Biobased superabsorbent polymers provide environmentally sustainable alternatives to fossil-based materials. They also offer effective moisture retention and absorbency for applications such as baby diapering, packaging, feminine hygiene, and adult incontinence products. It is also reported that the Archer Daniels Midland Company (ADM) has launched newest generation of biobased product such as BIOSAP (the company patented the technology of preparing using modified starch with similar technique of acrylic-based SAP preparation) – Lysorp 218 and Lysorp 220.

Few companies are catering to large part of the demand of global superabsorbent polymer market share. The key companies involved in this market which bear largest share include the BASF, Nippon Shokubai, Evonik, Sumitomo, and LG Chemical. Some other prominent companies also have significant share of market which include the Formosa Plastics, KAO Corporation, SDP Global Corporation, Yixing Danson Technology, and Songwon Industrial Corporation Limited.

3 Classification of Hydrogels

Hydrogels can be classified from various perspectives and depend on many factors. Properties of hydrogels are governed by the sources from where they are prepared. One of the specific aims of this classification is to make an understanding about the nature of hydrogels of biocompatibility, on the basis of sources from where they are originated:

(i) **Classification based on source:** Hydrogels are of mainly two groups according to their origin, i.e., natural and synthetic. Depending on the natural sources, this category includes collagen, fibrin, hyaluronic acid, Matrigel, and derivatives of natural materials such as chitosan, alginate, and silk fibers. On the other hand, hydrogels prepared from synthetic sources are mainly petrochemical based. As biocompatible hydrogel (i.e., biobased) carries extra emphasis according to the title, the author finds responsible to give brief discussion on biobased hydrogel in Sect. 3.1.

(ii) **Hydrogels based on polymeric composition:** The methods of preparation of hydrogels alter the types of product. The use of number of monomers gives hydrogels with different properties. Types of hydrogels based on polymeric composition are [21] described below:

Hydrogels from homopolymer: Polymeric network is formed from single monomer, and it is the fundamental structure on which the whole chain grows. The growing chain can also be cross-linked to alter properties by various polymerization techniques.

Hydrogels of copolymers: Hydrogels are formed by two or more different monomer species, among them at least one hydrophilic component arranged in a random, block, or alternating arrangement along the chain of the polymer network.

Hydrogels of interpenetrating polymeric network (IPN): This important class of hydrogels is prepared from two independent cross-linked synthetic and/or natural polymer components, arranged in a network form. In semi-IPN hydrogel, one component is of cross-linked polymer, and the other is a non-cross-linked polymer.

(iii) **Classification based on crystallinity:** Hydrogels are polymeric materials and gain various crystal structures during manufacture on the basis of technique applied. They are of mainly crystalline, amorphous, and combination of the previous two semicrystalline.

(iv) **Classification based on type of cross-linking:** Cross-linking is a common practice in hydrogel preparation. Two types of cross-linking are observed in hydrogels, chemical or physical. As a result, two types of networks are formed. In chemical cross-linking, the junctions formed are permanent, while in physical cross-linking, networks formed are fragile in nature. Transient junctions arise either from polymer chain entanglements or physical interactions such as ionic interactions, hydrogen bonds, or hydrophobic interactions.

(v) **Classification based on sizes:** Hydrogels can be given many expected shapes according to requirements and polymerization technique applied. The common shapes are film, microsphere, rounded, matrix, etc.

(vi) **Classification based on ionic particle:** Some hydrogels contain charged particles inside the polymeric chain and show conductive property. They can be divided into four classes depending on electrical charge available on the chain:
   (a) Nonionic
   (b) Anionic or cationic
   (c) Amphoteric electrolyte (ampholytic) containing both acidic and basic groups
   (d) Zwitterionic, containing both anionic and cationic groups in each structural repeating unit

(vii) **Classification based on mechanism during the drug release:** Hydrogels that are formulated for using in drug delivery system and their mechanism should be in controlled manner. It is of four types:
   (a) Release systems controlled by diffusion.
   (b) Release systems controlled by swelling.
   (c) Release systems controlled by chemical.
   (d) Release systems controlled by stimuli.

3.1 Biobased Hydrogels

Biobased hydrogels are mainly synthesized from natural sources which include mainly polysaccharides (e.g., cellulose, starch, chitosan, and natural gums such as xanthan, guar, and alginates) and protein (e.g., gelatin). Polysaccharide-based hydrogels are prepared either by graft copolymerization of monomers in presence of cross-linkers or direct cross-linking. Both processes give hybrid hydrogels. The first commercial polysaccharide-based hybrid hydrogel was starch-g-PAN, obtained by direct cross-linking [22]. The product showed path for conversion of other polysaccharides into hydrogels.

Hydrogels can also be formed from chitosan and its derivatives. Physical entanglement happens during curing at the temperature between 5 °C and 60 °C and within minutes to weeks time duration [23]. Derivatives of chitosan give better hydrogel product as it is soluble in water or acid. The hydrogel formation takes place either physical or by chemical cross-linking, and obtained hydrogel is thermoset and pH sensitive [24]. Sometimes chemical cross-linking is preferable due to stable structure and better swelling properties [25, 26]. By adding some synthetic part with natural polymer, composite or hybrid hydrogels with specific properties is obtained [27].

Not a good number but few works have been reported on hydrogels prepared from protein sources. In this regard, proteins from fish, soybean, and collagen are the three members which are practiced most frequently. It requires to modify the protein to convert it into hydrogel network [28]. Modified fish protein-based hydrogels showed the swelling capacity of 540 g/g in deionized water and assumed to be dependent on pH and ionic strength of swelling media and suggested for water absorption under load such as diapers [29].

Gelatin, collagen-based protein, and hydrolyzed collagen have been used for hydrogel preparation by graft polymerization of AA/AM, and the formed hydrogel is gelatin-g-poly (NaAA-co-AM). The hydrogel was high sensitive to pH [30].

Hydrogel preparation has been practiced with various natural sources due to sustainable factors, such as availability, low cost, easily processable, and biocompatibility. Cellulose is the best option for the researchers due to inheritance of the mentioned properties.

4 Factors Influencing Cellulose to Be Perfect Alternative for Sustainability

In principle, a product is said to be safe for sustainability when renewable, biobased materials are incorporated or made from such materials. Another perspective of sustainability is that the product goal is achieved with reduction in material consumption. It is well known that cellulose is renewable and biodegradable, and its derivatives are also highly biodegradable. Previously discussed requirements can be fulfilled by abundant renewable resource cellulose and its derivatives (Fig. 1a).

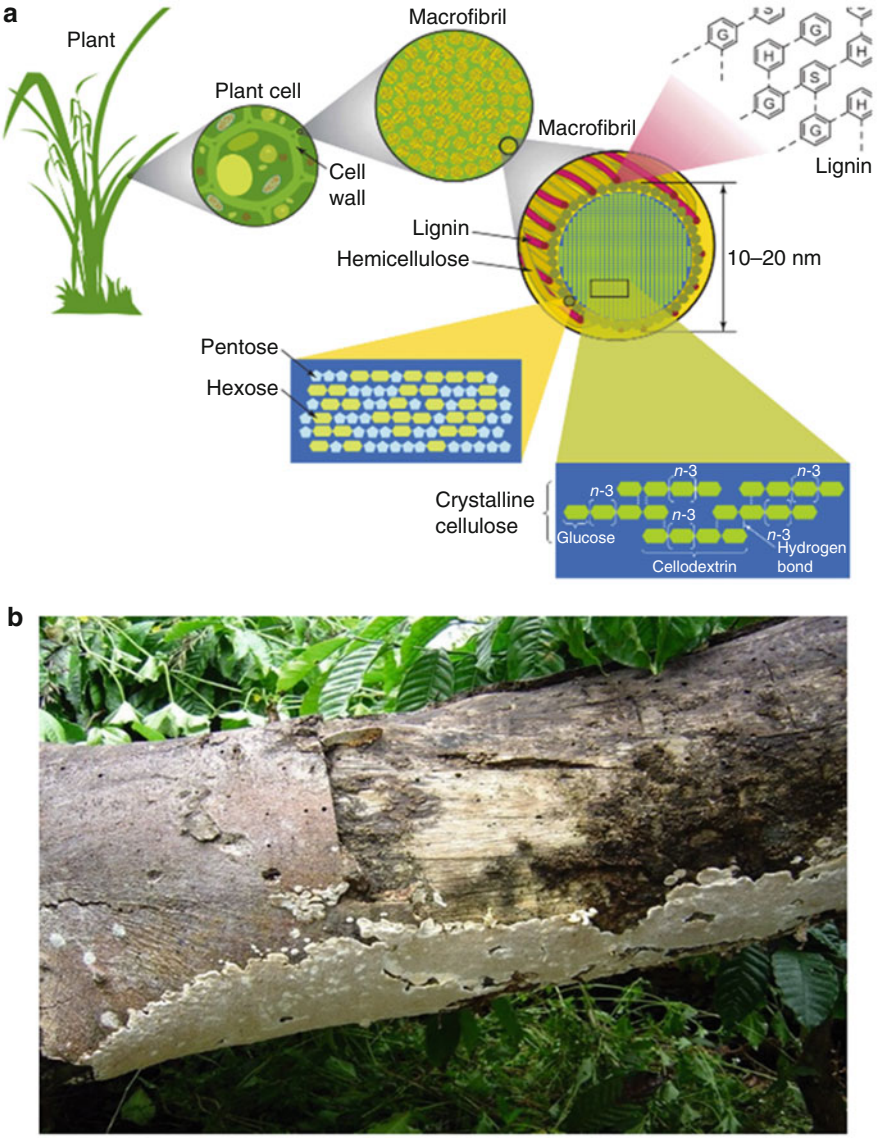

Fig. 1 (**a**) Indicates renewability of cellulose as it is the common ingredient of plant and (**b**) degradation of wood log by microorganism [36, 37]

Many researchers have been intentionally designed and tested to reach a suitable degree of biodegradability [25, 31]. Cost of materials is a key factor for consumer products, but conserving environment is more important. Hydrogels from non-renewable sources might be cheap, but lack of biodegradability gives scientists

motivation for development of cellulose-based and combination of cellulose and acrylic, hybrid hydrogels [32].

4.1 Unique Structure of Cellulose and Biodegradability

Cellulose is a polymer of glucose and also the main constituent of plants and natural plant fibers. It is found most abundantly in nature. Besides plants, some bacteria can also synthesize as extracellular product inside their body. Both the cellulose found in plant and bacteria are chemically identical but *different* in physical properties and molecular structure. The glucose units which are common for bacterial cellulose (BC) and plant cellulose (PC) are held together by 1,4-β-glycosidic linkages and responsible for higher crystallinity (usually in the range 40–60% for PC and above 60% for BC). Because of this, they are insoluble or partially soluble in water and other common solvents. BC can be synthesized and obtained fibers are nanosized, and about two orders of magnitude are smaller than PC fibers. For this BC cellulose shows a peculiar, ultrafine fiber network with high water-holding capacity and superior tensile strength compared to PC. Compared to PC, BC is found in pure form, and usually PC is associated with other biogenic compounds, such as lignin and pectin. As a result, to make in use, PC requires purification and modification. Modification via chemical change of cellulose is common which usually involves esterification or etherification of the hydroxyl groups. The chemical modification generally forms cellulose derivatives, named cellulosics. Cellulosics are easy to process and have numerous consumable applications. Cellulose and its derivatives are eco-friendly as they degrade by some bacteria and fungi present in air, water, and soil (Fig. 1b) [33]. The degradation process of cellulosic materials has been investigated by many researchers. Degradation process leads to decrease in molecular weight, lower mechanical strength, and lower degree of crystallinity and improved water solubility [34]. The abundance and degradation nature of cellulosic materials have trigger down the use of them in biomedical application [35]. As humans are unable to synthesize cellulose, they can't digest cellulose. The degradation of cellulose can be expressed as.

$$\text{Cellulose} \xrightarrow[\text{Hydrolysis}]{\text{Cellulase}} \text{Cellobiose} \xrightarrow[\text{hydrolysis}]{\text{Cellobiase}} \text{Glucose}$$

$$\text{Glucose} \xrightarrow{\text{Oxidation}} \text{Organic Acids} \xrightarrow{\text{Oxidation}} CO_2 + H_2O$$

4.2 Potentiality of Cellulose and Its Derivatives for Hydrogel Synthesis

The outer surface of cellulose is crystalline regions which can interact with water but unable to imbibe any water [38]. The amorphous region of cellulose and

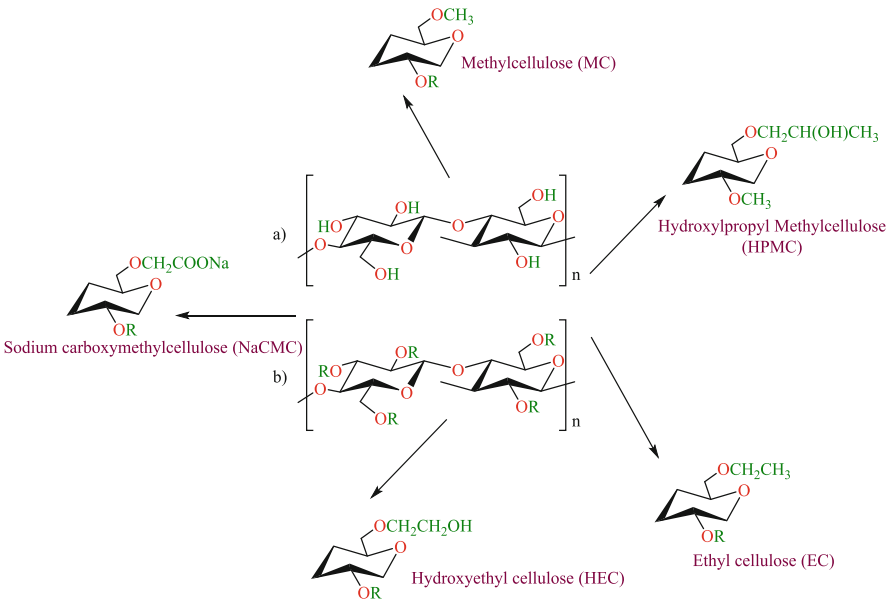

Fig. 2 (**a**) Repeating unit of cellulose, also termed "cellobiose." (**b**) Repeating unit of cellulose derivatives. The substituent group "R" is indicated for methylcellulose (MC), hydroxypropyl methylcellulose (HPMC), ethyl cellulose (EC), hydroxyethyl cellulose (HEC), and sodium carboxymethylcellulose (NaCMC)

hemicellulose can absorb water and swell [39]. Derivatization of cellulose makes it more biodegradable. The reaction of the hydroxyl groups of cellulose with organic species, such as methyl and ethyl units, gives most water-soluble cellulose derivatives via etherification. Cellulose derivatives with given solubility and viscosity in water solutions can be obtained by controlling the degree of substitution (as the average number of etherified hydroxyl groups in a glucose unit). The most widely used cellulose derivatives are cellulose ethers, such as methylcellulose (MC), hydroxypropyl methylcellulose (HPMC), ethyl cellulose (EC), hydroxyethyl cellulose (HEC), and sodium carboxymethyl cellulose (NaCMC). Figure 2 represents the chemical structure of cellulose and its derivatives. Many researchers have synthesized hydrogels from the abovementioned cellulose derivatives [25, 31]. NaCMC, among the other cellulose derivatives, is polyelectrolyte in nature, shows sensitivity to pH and ionic strength variations, and thus is a "smart" cellulose derivative. Due to a Donnan-type effect [40], the polyelectrolyte nature of NaCMC assists NaCMC-based hydrogels a double effect on the swelling capability.

Synthesis of cellulose-based hydrogels involves either physical or chemical stabilization of aqueous solutions of cellulosics. During synthesis, addition of natural or synthetic monomers or polymers gives composite hydrogels with

specific properties [41, 42]. The polymer network can be formed in both physical and chemical means. In physical network formation, hydrophobic association of polymer chains takes place at low temperature. At higher temperature, macromolecules gradually lose their water of hydration, entangled with one another, and hydrogel network is formed. Physically cross-linked hydrogels have some drawbacks like degrade in uncontrollable manner, and reversibly [43] for this, they cannot be applied in many fields (e.g., biomedical application). The ill points of physically cross-linked hydrogels of cellulose derivatives (MC and HPMC) can be replenished by inducing the formation of chemical, irreversible cross-links among the cellulose chains. The degree of cross-linking which affects many properties (diffusive, mechanical, and degradation) can be controlled in required extent during synthesis. In some cases, chemical modifications of the cellulose backbone might be performed before cross-linking, in order to obtain stable hydrogels with given properties [44]. Some cross-linking agents are toxic in nature. Taking into consideration environmental and health safety concerns, radiation cross-linking of polymers, based on gamma radiation or electron beams, has been receiving increasing attention in the last couple of years. The irradiation technique is governed by irradiation dose as well as by the cellulose concentration in solution [45–47]. As radiation treatment does not involve additional chemical reagents, is easily controllable, gives some benefits to biomedical applications, and allows the simultaneous sterilization of the product, the researchers are more interested to apply in hydrogel preparation.

4.3 Biocompatibility of Cellulose-Based Hydrogels Over Synthetic Hydrogels

Hydrogels manufactured from nonrenewable petrochemical sources are available in the market, and consumers are familiar with the products. With unconscious mind of the consumers after the end use, the thrown debris with hydrogels are making the environment more intolerable. The reason behind this is nondegradable nature of currently available hydrogels. If the petrochemical-based hydrogels are degraded by any means, the degraded products are gaseous and toxic to both human being and animals including environment. As cellulosics are more environment friendly, the hydrogels originated from them should also be biodegradable in nature [33]. In addition to biocompatible factor, the world petroleum source is limited compared to renewable cellulose and its derivative sources. It has been largely investigated by many researchers that cellulose and its derivative-based hydrogels degrade by cellulose enzyme, which is unable toward noncellulosic hydrogels [34]. This suggests cellulosic hydrogels can be used in biomedical application. Cellulose and its derivatives have many widespread perspectives and contribute positive attitude toward enhanced absorption performance of hydrogels. It has also been reported that introduction of cellulose not only increases the biodegradability but also absorption (up to 2500 g/g) [48] and other performances.

5 Methods of Preparation of Cellulose-Based Hydrogels

In a very simple sense, hydrogels are hydrophilic polymeric network cross-linked in some fashion to produce elastic structures. As a result, any suitable technique can be used to create a cross-linked polymer to produce a hydrogel. Among various techniques, copolymerization/cross-linking free-radical polymerizations are commonly used to produce hydrogels by reacting hydrophilic monomers with multifunctional cross-linkers. By using any of the polymerization techniques (bulk, solution and suspension polymerization), the formation of the gels is possible. The integral components of whole process of hydrogel formation are monomers, initiators, and cross-linking agents. In addition, diluents like water or other aqueous solutions can be used to control the heat of polymerization. In the final stage, the end product requires washing to remove impurities left from the preparation process like non-reacted monomer, initiators, cross-linkers, and unwanted products produced via side reactions showed in Fig. 3b as a general scheme for preparation. In this respect, water-soluble monomers from both natural and synthetic origins are polymerized and then cross-linked to form hydrogels in a number of ways:

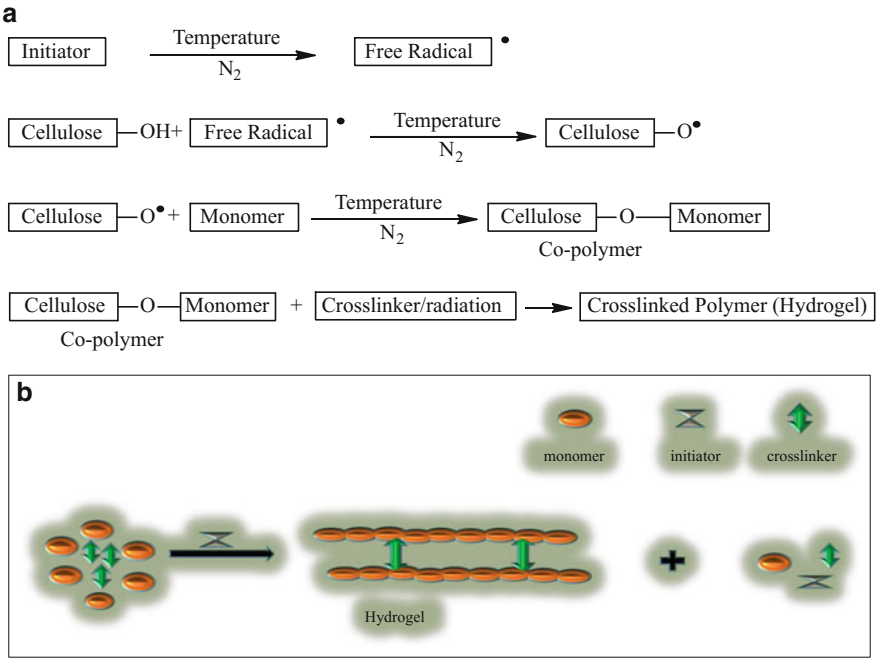

Fig. 3 (**a**) General scheme for hydrogel preparation and (**b**) schematic diagram for hydrogel preparation

1. Attachment of polymer chains via chemical reaction
2. Generation of main chain free radicals using ionizing radiation which can recombine as cross-link junctions
3. Physical interactions such as entanglements, electrostatics, and crystallite formation within chains

Considering environmental protection and to establish the thought that partially or complete replacement of synthetics by greener alternatives, cellulose gaining the prime importance to synthesis hydrogels [49]. The most important polysaccharides (chitin, cellulose, starch, and natural gums) are the cheapest and most abundant, and renewable organic materials are available. Among them cellulose is most abundant in nature. Generally two types of chemical reactions are performed for the synthesis of cellulose-based hydrogels: (a) in the presence of a cross-linker graft copolymerization of suitable vinyl monomer(s) on polysaccharide (cellulose) and (b) polysaccharides which are directly cross-linked.

To obtain hydrogel through graft copolymerization, generally a polysaccharide (cellulose) interacts with initiator by either of the two separate ways. In first case, the neighboring OHs on the saccharide units and the initiator (commonly $Ce^{4+)}$ interact to form redox pair-based complexes. Subsequently these complexes are dissociated to produce carbon radicals on the polysaccharide substrate via homogeneous cleavage of the saccharide C–C bonds. Created free radicals initiate the graft polymerization of the vinyl monomers and cross-linker on the substrate. On the other hand, in the second case, an initiator such as persulfate may abstract hydrogen radicals from the ~OHs of the polysaccharide to produce the initiating radicals (oxygen radicals) on the polysaccharide backbone (Fig. 3a). As these are thermal initiators, this reaction is more temperature sensitive compared to other methods.

In case of direct cross-linking of polysaccharides (cellulose), various cross-linking agents were employed like polyvinyl compounds (e.g., divinyl sulfone, DVS) or polyfunctional compounds (e.g., glycerol, epichlorohydrin, and glyoxal) [22, 50]. Most recently $POCl_3$ and citric acid have been used to synthesize natural cellulosic hydrogels [51, 52]. The overall polymerization technique was shown schematically in Fig. 3b.

6 Characterization of Hydrogels Through Analytical Technique

Physical and chemical characterizations of hydrogels both are essential for academic and industrial applications. The following tests are conducted to characterize the hydrogels. Some experiments related to physical characterization are as follows.

6.1 Free-Absorbency Capacity

Absorption capacity is a common but fundamental property of hydrogel. When the term swelling and absorbency are used without specifying its conditions, it implies

uptake of distilled water, while the sample is freely swollen, i.e., without applying load on the test sample. Several simple methods for the free absorbency test are available. These methods are dependent mainly on the amount of the available sample, the amount of water absorbed by the sample, and the method's precision and accuracy. Among various methods mostly followed are *tea bag method*, *centrifuge method*, and *sieve method*. Tea bag method is simple and fast, but sieve method requires a large amount of sample (1–2 g). On the other hand, the measured values in centrifuge method are often more accurate, reliable, and lower than those obtained from the tea bag method values due to removal of interparticle liquid. For convenience, only *tea bag method* is discussed below.

6.1.1 Tea Bag Method

For limited amounts of samples, this method is the most convenient, fast, and suitable ($M_0 = 0.1$–0.3 g, sample weight) [53–55]. The hydrogel sample is placed into a tea bag (acrylic/polyester gauze with fine meshes), and the bag is dipped in an excess amount of water or saline solution for 1 h to reach the equilibrium swelling. Then excess solution is removed by hanging the bag until no liquid is dropped off. The tea bag is weighed (M_1), and the swelling capacity is calculated by Eq. (1). The method's precision has been determined to be around ±3.5%.

$$\mathrm{Se} = (M_1 - M_0)/M_0, \tag{1}$$

where Se is the equilibrium swelling capacity

Centrifuge method is more accurate than the tea bag method and is occasionally reported in patents and data sheets [20]. Sieve method requires a large amount of sample (1–2 g) and is also called filtering and rubbing method [56].

6.2 Absorbency Under Load

The absorbency under load (AUL) is also another representation of absorption data which is more reliable and authentic. Because of this, usually it is given in the patent literature and technical data sheet by industrial hydrogel (SAP) manufacturers [57]. The AUL is generally measured under some specified conditions but without specifying its swelling media. The process measures an uptake of 0.9% NaCl solution, while the test sample is pressurized by some loads (often specified to be pressures 0.3, 0.6, and 0.9 psi). For testing, a typical AUL tester (Fig. 4) is a simple but finely made device including a macro-porous sintered glass filter plate (porosity # 0, d = 80 mm, h = 7 mm) placed in a petri dish (d = 118 mm, h = 12 mm). During experiment, the weighed dried hydrogel sample (0.90 ± 0.01 g) is uniformly placed on the surface of polyester gauze located on the sintered glass. To apply load, a cylindrical solid load (Teflon, d = 60 mm, variable height) is put on the dry hydrogel particles, while it can be freely slipped in a glass cylinder (d = 60 mm, h = 50 mm). For the calculation of AUL, desired load (applied pressure 0.3, 0.6, or 0.9 psi) is placed on the hydrogel sample (Fig. 4), and saline solution (0.9% NaCl) is added up

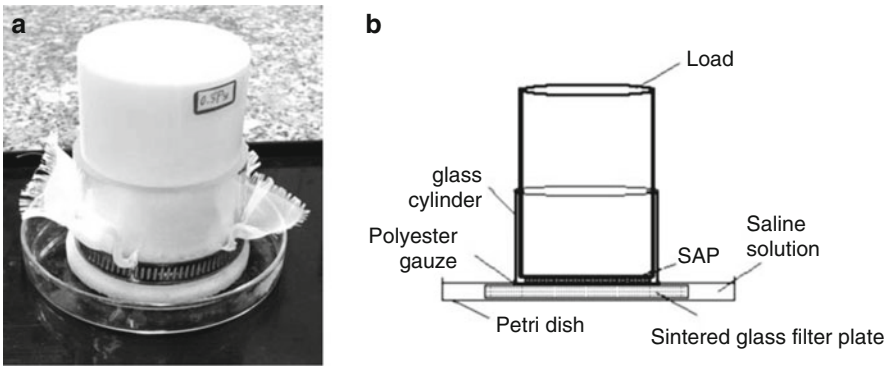

Fig. 4 (**a**) A typical AUL tester picture and (**b**) various parts [59]

to the height of the sintered glass filter. To prevent surface evaporation and probable change in the saline concentration, the whole set is covered. The swollen particles are weighed again, and AUL is calculated after 60 min, using Eq. (2):

$$\mathrm{AUL}_{(g/g)} = \frac{M_2 - M_1}{M_1} \tag{2}$$

where M_1 and M_2 denote the weight of dry and swollen SAP, respectively. The AUL indicates the swollen gel strength of SAP materials [58].

6.3 Wicking Capacity and Rate

The wicking capacity (WC) of SAP (hydrogels) materials is a measurement of capillary action. To quantify this, a simple test has been suggested by pioneering researchers Fanta and Doane [60] with conventional physical appearance, i.e., sugar-like particle. The test is accomplished as hydrogel sample ($M_1 = 0.050 \pm 0.0005$ g) is added to a folded (fluted) filter paper cone prepared from an accurately tared circle of 9 cm Whatman 54 paper. To settle the sample into the tip, the cone was lightly tapped, and the tip of the cone is then held for 60 s in a 9 cm Petri dish containing 25 mL of water. Within a minute, water wicks up the entire length of the paper, and excess water is allowed to drain from the paper by contacting the tip for 60 s with a circle of dry filter paper on a square of absorbent towel. For calculation, weight of wet paper plus swollen polymer is determined (A), and the absorbency of the sample in g/g is then determined after correcting for the weight of dry paper and the amount of water absorbed under identical conditions by the paper alone in the absence of sample (Eq. 3). Repetition for 3–5 times each test is preferred and the results are averaged.

$$\mathrm{WC} = (\mathrm{A} - \mathrm{B} - \mathrm{M}_1)/\mathrm{M}_1 \tag{3}$$

where B is weight of wet paper without polymer.

Assuming a steady absorption for the duration of 60 s, an estimation of wicking rate (g/g.s) of the hydrogel may be obtained by dividing the WC value by 60.

6.4 Swelling Rate

Swelling rate is also an important parameter for determining quality of manufactured hydrogel. It can be calculated in a number of ways. Among them two common methods are *vortex method* and *swelling-time profile*. Vortex method is the most simple and rapid method for calculating swelling rate of hydrogel sample and is often employed in R&D and technical laboratories [61]. For a conceptual understanding, *swelling-time profile* is described below.

6.4.1 Swelling-Time Profile

Actually this is a graphical representation of swelling versus time and is obtained via separating swelling measurements of sample absorbed desired fluid at consecutive time intervals. For swelling measurement, any of the methods (tea bag, centrifuge, or sieve methods) can be used for the measurements depending on the amount of the available sample and the desired precision. This profile is helpful to the study of swelling kinetics of hydrogels. In a measurement, several 2 L Erlenmeyer flasks containing distilled water or desired solution are labeled, and SAP sample (e.g., 1.0 g, 50–60 mesh) is poured into each flask and is dispersed with mild stirring. The absorbency of the sample is measured by the abovementioned method at consecutive time intervals (e.g., 15, 30, 45, 60, 90, 120, 180, 300, 600, 1800 s). A typical profile is shown in Fig. 5.

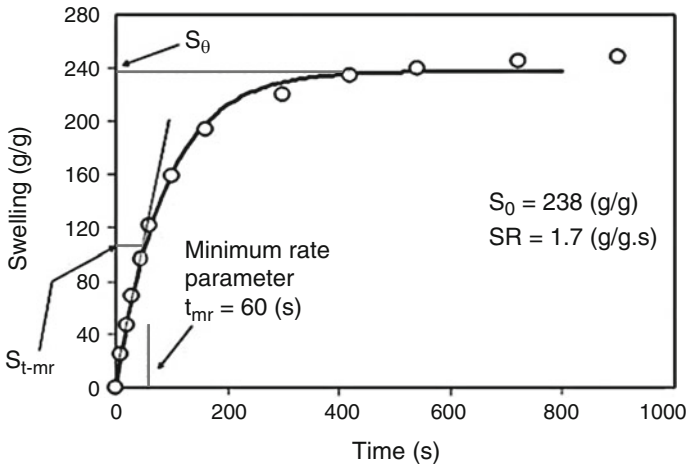

Fig. 5 Representative curve for swelling kinetics of a hybrid SAP sample in distilled water [61]

6.5 Swollen Gel Strength

From a practical viewpoint in specified area of application, the mechanical strength or modulus of swollen SAPs (hydrogels) is important. Rotational rheometry can be an important tool to quantify the swollen gel strength of hydrogels with conventional shape, i.e., sugar-like particles [62]. The method works by using parallel plate geometry (plate diameter of 25 mm, gap of 3 mm) at 25 °C. The strain suggested for the experiment is to be in the linear viscoelastic (LVE) range, where the G' and G'' are independent of the strain amplitude. Frequency test sweeps are done after a strain sweep test, and the test conditions are selected to ensure that the test is really carried out in the LVE range. In the determination of LVE, approximately 100–150 mg of dried SAP with average particle sizes of 180 μm is dispersed in 200 mL of distilled water for 30 min to reach maximum swelling. The swollen gel particles are made free of excess water and then placed on the parallel plate of rheometer, and the rheological properties are evaluated.

6.6 Soluble Fraction

Soluble fraction (sol) for a hydrogel is an important criterion. It is a sum of all water-soluble species including non-cross-linked oligomers, β-hydroxypropionic acid (HPA), and non-reacted starting materials such as residual monomers. The amount is simply measured by extraction of hydrogel sample in distilled water (because of this, the sol is frequently referred to "extractable"). For calculation, a certain amount of the hydrogel sample (e.g., 0.10 g) is poured into excess amount of water and dispersed with mild magnetic stirring to reach equilibrium swelling (0.5–3 h depending on the sample particle size), filtering the sample after swelling and dried in oven. The weight loss of the sample is the soluble fraction. The gel content which is also important for a synthesized hydrogel can also be obtained by simple Eq. (4). The equation indicates that gel content may be taken as an actual yield of the cross-linking polymerization.

$$\text{Sol}\ (\%) + \text{Gel}\ (\%) = 100 \tag{4}$$

6.7 Residual Monomer

Residual monomer content is of very significant in case of hydrogel materials, particularly SAPs used in hygiene product where the residual acrylic acid should be in safe level. To quantify residual monomer, high-performance liquid chromatography (HPLC) is often taken as a preferred method. Orthophosphoric acid solution is usually used as an extractant for this method. The total residual monomer is removed in form of either acid or salt from the hydrogel network and is measured in the next step. At lower pH, the acrylic salt is converted to acrylic acid both the extracting and the eluting media, i.e., mobile phase (pH < 3) [63]. Isocratic mode at

a 1.8 mL/min flow rate and ambient temperature on an analytical column (e.g., 250 × 4.6 mm, 5 μm) are used for separation. An aqueous 0.01% orthophosphoric acid is used as the mobile phase [64]. UV-Vis absorbance can also be used to serve the purpose, in that case over the 190–400 nm range is registered and the wavelength used is 200 nm.

6.8 Ionic Sensitivity

It is a measure of sensitivity of hydrogel materials toward the kind of aqueous fluid absorbed. To quantify a dimensionless swelling, factor, *f*, is defined as follows (Eq. 5) [65]:

$$f = 1 - (\text{absorption in a given fluid}/\text{absorption in distilled water}) \quad (5)$$

For better performance, hydrogels with lower *f* are usually preferred, as higher *f* value indicates the higher absorbency loss of the sample swollen in salt solutions. Negative values of *f* are rare but happen, which reveal that the absorbency is not decreased, but it is increased in salt solutions. It is reported that the hydrogels with betaine structures exhibit such surprising behavior [53].

In addition to physical characterization, the synthesized product requires structural confirmation so that their application becomes flawless. Few relevant instrumental analyses give reliable data for the product. The commonly used instrumental techniques are briefly discussed.

6.9 FTIR Analysis

The observation of functional groups present in samples within the frequency range from 400 to 4000 cm^{-1} is generally used. Finely ground samples are mixed with KBr and pressed to form a KBr pellet. The FTIR spectra of sample (generally a characteristic peak of fuctional groups at specified wavelength) is observed by the method of transmission. This method supplies sufficient data by forming relevant peak to ensure about the functional groups that formed during reaction.

6.10 TGA and DSC

Thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC) are two reliable tools for the thermal analysis of the product. During decomposition, exothermic or endothermic nature of the hydrogel sample can be examined. TGA determines selected characteristics of materials that exhibit either by mass loss or gain due to decomposition, oxidation, or loss of volatiles (such as moisture). On the other hand, DSC measures the difference in the amount of heat required to increase the temperature of a sample and reference as a function of temperature.

6.11 SEM, TEM, and AFM

Surface morphology of the prepared hydrogels can be observed by SEM analysis. Transmission electron microscopy (TEM) and atomic force microscopy (AFM) are also two helpful tools for the study of surface morphology with high resolution. In case of SEM, the micrographs were taken at a definite magnification using (kV) accelerating voltage to observe the surface construction.

On the other hand, TEM is capable of imaging at a significantly higher resolution than light microscopes and can capture fine detail – even as small as a single column of atoms. TEM is also used to observe modulations in chemical identity, crystal orientation, electronic structure, and sample-induced electron phase shift as well as the regular absorption-based imaging. AFM serves three information about the product; force measurement determines physical properties like stiffness, image formation of the three-dimensional shape (topography) of a sample surface at a high resolution, and manipulation of forces used to change the properties of the sample in a controlled way.

6.12 XRD Analysis

X-ray diffraction (XRD) method is used to study the structure, composition, and physical properties of materials. It is a rapid analytical technique for phase identification of a crystalline material and can provide information on unit cell dimensions. XRD gives the idea of crystalline and amorphous region of the sample. One can predict about the nature of the product, how it has been transformed from one phase to another.

All diffraction methods rely on generation of X-rays in an X-ray tube. These X-rays are directed at the sample, and the diffracted rays are collected for analysis of specimen. An important factor of all diffraction is the angle between the incident and diffracted rays.

6.13 Biodegradability Test

Decomposition data carries immense importance for cellulose-based product. As it is mentioned earlier, biocompatible products are those when thrown to the environment decomposed by microorganism and leave nothing harmful for human being or animals. The two mostly exercised degradation tests are soil burial test and direct microbial studies. In the case of soil burial test, the test specimen is buried in soil, and after definite time interval, the sample is washed and weighted. The result is expressed as percent weight loss for specific time duration. At the same time, direct microbial studies also determine weight loss of the product, but the decomposition is carried out in presence of direct contact of cultured microorganism.

7 Application of Cellulose-Based Hydrogels and Their Biocompatibility

It is a proven truth that synthetic hydrogels have some better qualities, but when biodegradability or eco-friendliness of a hydrogel is required or recommended, cellulosics are prime choice hydrogel precursor materials, due to their low cost,

the large availability and biocompatibility of cellulose, and the stimuli-responsive properties. Current research has unveiled the fact that cellulose-based hydrogels cannot be complete replacement of synthetic hydrogels but would be the most potential competitor. Some of the recent and conventional uses of cellulose-based hydrogels have been discussed below.

7.1 Hydrogels for Personal Hygiene Products

The recent trend is to use acrylate-based superabsorbent hydrogels in personal hygiene product to absorb body fluids. These products keep individuals dry and ensure healthy skin and personal comfort. It is observed that the majority of parents in developed countries, along with thousands of hospitals and day care centers around the world, use disposable diapers containing a superabsorbent polymer (SAP) for the infant. The use of SAP material in training pants and adult incontinence products is increasing day by day worldwide. In recent years, a number of papers have been published in the favor of the use of superabsorbent materials in personal care products and their safety and effectiveness [66, 67]. The leakage of diapers is very significant to raise the risk of fecal contamination and spread of illness in day care play areas [68]. The SAP helps control the spread of germs keeping the skin dry and preventing diaper rash. Now it is a true fact through several medical studies that disposable diapers play an important role in reducing the risk of spread of gastrointestinal illnesses and are significantly more effective than double cloth diapers and plastic overpants [69]. Although Harper [70] and Harmon [71] separately patented their superabsorbents in 1966, superabsorbent was used for the first time in diaper industry by the Unicharm in 1982 in Japan, following its use in sanitary napkins. The superabsorbent materials introduced a new generation of high-performance diapers. It made the diapers not only thinner but also improved retention performance compared to cloth diaper which helped reduce leakage and diaper rash [72]. In this regard, premium diapers reduced leakage values and the average weight by below 2% and about 50%, respectively. Considering environmental and economic issue, the reduction of packaging cost was advantageous. For better understanding the current ecological impact of disposable diapers and other similar articles, it is substantial to provide a brief estimate of diaper consumption. In a published article, it has been shown that a child till the age of 30 months uses approximately six disposable diapers a day. If a diaper has an average volume of 500 cc, so one child produces on average 3000 cc of garbage a day, i.e., 1.092 cubic meters per year. As it is considered that there are about 50,000 diaper users per million population, every day it would be necessary to remove 1500 cubic meters of diapers from a city of one million inhabitants. Taking into account the benefit of recycling, different attempts have been made to recycle disposable diapers, napkins, hospital bed sheets, sanitary towels, and other similar products [73]. The structure of all these cellulose-containing products is almost the same: an envelope of non-woven tissue, a plastic cover material, and an absorbent fluff of wood pulp cellulose, mixed in most cases with SAP. The main objective of diaper recycling is to recover

separately the cellulose, which is biodegradable and recyclable, the plastic cover material, and the SAP, both of which are not biodegradable but might be recycled for other uses. The difficulties during recycling process have prompted the parallel development of biodegradable diapers, i.e., possessing a biodegradable SAP. An alternative solution has been found to replace SAP by cellulose-based hydrogels, which are totally biodegradable. Sodium carboxymethylcellulose (NaCMC)- and hydroxyethyl cellulose (HEC)-based novel hydrogels cross-linked with divinyl sulfone (DVS) possess swelling capabilities comparable with those displayed by SAP and high water retention capacities under centrifugal loads. Cellulose-based hydrogels show some advantages over current SAP that encompasses their biodegradability and environment-friendly nature. In this respect, recent innovations and total success of the cellulose-based hydrogels described above depend on the implementation of an eco-friendly production process [74] and the use of nontoxic cross-linking agents [75, 76]. Radiation technique for cross-linking instead of using chemicals might be a valuable alternative in the development of novel environmentally friendly superabsorbents.

7.2 Water Conservation in Agriculture

Due to continuous deficiency in surface water, the interest of using superabsorbent hydrogels in agriculture is increasing. Another important objective is to reduce water consumption and optimize water resources in agriculture and cultivation. Research articles have been published in the promotion of using a novel material to replace human habit and culture toward water so that it can be benefited to save and not make an excess to waste. It is well known to all that during the swelling process of a hydrogel, the material turns from solid to a gel-like material, which is able to store large volume of water even under significant compression. Consequently the swollen hydrogel can slowly release up-taken water through a diffusion-driven mechanism, if a gradient of humidity exists between the inside and the outside of the material. In addition up-taken water and other ingredients can be released in a controlled and sustained manner by means of diffusion. In arid and desert regions of the world, where scarcity of water resources is a burning issue, the xerogel (i.e., dry hydrogel), in the form of powder or granules, is spread in the area close to plant roots. The hydrogel can also be loaded with nutrients and/or plant pharmaceuticals. At the time of cultivation, water or nutrients mixed water is sprayed; the water is absorbed by the hydrogel, which then releases to the soil as needed, thus keeping the soil humid over long periods of time. The use of hydrogels in cultivation allows a high saving of water, which is not lost soon after the watering due to evaporation and drainage. Such distribution of the water resources available for cultivation can be used for other applications. Another observation of using hydrogels is that the swelling with water itself on the soil increases volume of dry hydrogels, and this increased volume of hydrogels changes the dimension, resulting increasing soil porosity and providing a better oxygenation to the plant roots. The aeration mechanism also suggests that large-granule hydrogels are likely to yield better results than fine-granule ones, if

properly mixed with the soil. A number of commercially available products are able to absorb, retain, and release water to the soil. It has also been proven that all these products are effective in water conservation due to their extremely high water retention capacity for cultivation. It is also reported that overdosage of such products is potentially dangerous and should be avoided. Yet enough research studies have not been carried out to determine appropriate amounts of hydrogels and application rates for different environmental conditions and different plant species [77]. It is worth mentioning that being acrylate-based, most commercial products are not biodegradable. Cellulose-based hydrogels can be the perfect alternatives to the recent trend of acrylate-based superabsorbent hydrogels. It is reported that Sannino and coworkers recently developed a novel class of totally biodegradable and biocompatible microporous cellulose-based superabsorbent hydrogels [9, 78–80], and such products are able to absorb up to 1 l of water per gram of dry material, without releasing it under compression. It is possible that hydrogel can be prepared both in form of powder and of a bulky material with a definite shape and a strong memory of its shape after swelling. The hydrogel can be entrapped with small molecules, such as nutrients, to be released under a controlled kinetic. Among the various applications of this material, a study has been performed on its specific use as water conservation in agriculture. Sorption capacity of hydrogel has been tested at different ionic strength of the swelling medium, with the expected target to simulate as much as possible the hydrogel-soil interaction. A pilot-scale production plant has been developed to prove the feasibility and the efficacy of the proposed technology and to produce the amount of hydrogel necessary for some studies being carried out in experimental greenhouses in the south of Italy, where the scarcity of water is a common problem. Early experimental results show great achievement. The soil with small quantities of the hydrogels is able to remain humid for periods more than four times longer compared to the soil watered without the presence of the hydrogel. When mixing the soil with a fine-granule gel, air flow is limited, and a layer of substrate/gel mixture might form, which further limits the flows of air and water within the soil. With a large-granular gel, a better air flow through the soil is yielded, resulting in higher oxygenation to plant roots. As the added cellulose-based hydrogels are biodegradable in nature and will decompose in soil at the end of its action, it will not make any adverse effect to soil or environment.

7.3 Body Water Retainers

Cellulose and cellulose derivatives are biocompatible, and hydrogels originated from them also show this property. In addition, they display versatile properties which suggest their use in biomedical applications. As hydrogels swell in water, cellulose-based hydrogels can be used as devices for the removal of excess water from the body, in the treatment of some pathological conditions, such as renal failure and diuretic-resistant edemas. In time of treatment, the hydrogel in powder form is taken up orally and absorbs water in its passage through the intestine, where the pH is about 6–7, without previously swelling in the acid environment of the stomach. The

hydrogel is then expelled through the fecal way, thus performing its function without interfering with body functions. Cellulose hydrogels, based on NaCMC and HEC, have been investigated for such applications [81] due to pH sensitivity. This type of application is in research level, sufficient data are not available, but petroleum-based hydrogels might show toxic effect compared to cellulosic hydrogels.

7.4 Stomach Bulking Agents

From the findings of the World Health Organization, at least one in three of the world's adult population is overweight and almost one in ten is obese. Moreover, there are over 20 million children under age 5 who are overweight. Obesity and overweight are responsible for several chronic diseases, such as type 2 diabetes, cardiovascular disease, sleep apnea, hypertension, stroke, and certain forms of cancer. It is also found that overweight or obese often has a dramatic impact on the psychological well-being, reducing the overall quality of life [82–84]. The treatment of overweight and obesity generally includes supervised diet or dietary supplements and is combined with adequate physical exercise. In the most cases, dietary supplements are claimed to act either by binding fats and so reducing fat absorption by human body or by directly reducing the appetite, which is done by absorbing liquids and swell inside the stomach, thus giving a sense of fullness [85, 86]. The first pathway is reported for chitosan-based products and the next for different natural fibers and herbal products. The natural fibers and herbal products use natural fillers or bulking agents that are very interesting for its great potential of reducing the amount of food intake by reducing the available space in the stomach. Though there is no clear evidence of the effectiveness of currently available bulking agents in promoting weight loss, neither in the short term nor in the long term, whereas their adverse effects, one should be taken into account the harmful effect of the products. Some hydrogels have required properties so that they can serve the purpose of using a stomach bulking agent. It is reported that novel cellulose-based hydrogels, obtained by cross-linking aqueous mixtures of NaCMC and HEC, have been shown to be appealing for the production of dietary bulking agents [87]. The polyanionic nature of the NaCMC hydrogels provides higher swelling capabilities at neutral pHs rather than at acid ones; the swelling ratio obtained at acid pHs might still be significant for use of the hydrogel as stomach filler where the environment is acidic. Indeed cellulose-based hydrogels obtained from nontoxic cross-linking agents are particularly attractive for this kind of application [52].

7.5 Devices for Controlled Drug Delivery

Among various cellulose derivatives, cellulose ethers (e.g., hydroxypropyl methylcellulose (HPMC)) have long been used in the pharmaceutical industry as excipients in many drug formulations [88]. These materials work as active ingredient carrier; they swell in presence of body fluids and release the drug molecule later. In the

progress of swelling at certain period, the drug dissolves in water and diffuses out from the polymer network. The rate of drug release from hydrogel depends on the water content of the swollen hydrogel, as well as on its network parameters, i.e., degree of cross-linking and mesh size [89, 90]. In recent time not only the swelling tablets but also more sophisticated hydrogel-based devices have also been developed for controlled drug delivery. In some cases, they are not only taking less time but also can function at a specified site. The loading of the drug in a hydrogel is performed either after cross-linking or simultaneously during network formation. Smart hydrogels modify the mesh size of the hydrogel network by responding in physiologically relevant variables, such as pH, temperature, and ionic strength, and are particularly useful to control the time- and space-release profile of the drug. Cellulose-based polyelectrolyte hydrogels (e.g., hydrogels containing NaCMC) are particularly suitable for the application of oral drug delivery which is usually based on the strong pH variations encountered when transitioning from the stomach to the intestine. Anionic hydrogels based on carboxymethyl cellulose have been investigated recently for colon-targeted drug delivery [91]. The most recent practice of controlled release through a hydrogel matrix dealt with the delivery of proteins, growth factors, and genes to specific sites, the need for which has been prompted by tissue engineering strategies. The direct delivery of drugs or proteins to different body sites requires the hydrogel biodegradation, in order to avoid foreign body reactions and further surgical removal. Injectable hydrogel formulations are particularly appealing and currently under investigation. In this case, the cross-linking reaction has to be performed under mild conditions in order not to denature the loaded molecule. Injectable formulations of hydrogels based on HPMC have been developed to deliver both biomolecules and exogenous cells in vivo [92]. The microenvironment resulting from degradation of the polymer should be mild. Change is the mesh size of the network, which determines the free space available for diffusion and thus regulates the diffusion of molecules (e.g., drugs) through the network itself. From the above discussion, it is mentionable that petroleum-based hydrogels may include toxic effect inside the body and may remain as part of the body which requires surgery. So cellulose-based hydrogels are suitable than petroleum-based nondegradable and non-biocompatible hydrogels.

7.6 Scaffolds for Regenerative Medicine

Regenerative medicine is a branch of translational research in tissue engineering and molecular biology which deals with the induced regeneration of cells, tissues, and organs in vivo, by means of a scaffolding material or template that guides and supports the cells during the synthesis of new tissues. Cellulose-based hydrogels have large water content capacity, are biocompatible, and possess rubbery mechanical properties close to those of soft tissues and usually allow the incorporation of cells and bioactive molecules during the gelling [93]. During regeneration, adhesion problem of cells to highly hydrophilic surfaces can be easily modified with extracellular matrix (ECM) domains of hydrogels, which promote cell adhesion as well as

specific cell functions [94]. This property gave opportunity to scientist to consider hydrogels for the design of biomimetic scaffolds for tissue regeneration. In the last decade, the excellent biocompatibility and good mechanical properties of cellulose and its derivatives have received increasing attention, as biomaterials for the design of tissue engineering scaffolds. It has been published that cellulose and its derivatives can be applied as scaffold material for the treatment of severe skin burns and in the regeneration of cardiac, vascular, neural, cartilage, and bone tissues [95–98]. A few independent investigations show that cellulose-based hydrogels are potentially useful for inducing the regeneration of bone, cartilage, and neural tissues. From the various research, it has been pointed out that as the final product of cellulose degradation is glucose, which is a nutrient for cells, there are the advantages in using cellulose rather than other synthetic or natural polymers for tissue engineering applications. Independent investigations have reported that novel biomimetic hydrogels, based on cross-linking cellulose derivatives with hyaluronic acid (HA), show potential as scaffolds for regenerative medicine, with a tunable degradation rate. The degradation rate is dependent on the amount of degradable sites as well as the degree of cross-linking of the network, which affects enzyme diffusivity through the mesh size. The degradation nature of the cross-linking agent used is particularly important, especially in cases where reactive groups of the cross-linker are incorporated into the hydrogel network and might then be released upon degradation. Recently hydrogels based on HEC, NaCMC, and HA have been cross-linked with a water-soluble carbodiimide, which is both nontoxic and a "zero-length" cross-linker. It is also reported that the carbodiimide washed out from the polymer network after the synthesis; thus cellulose-based hydrogels cross-linked with carbodiimide show potential for a tunable biodegradation rate, even without containing HA [99]. Although biodegradation behavior of hydrogels cross-linked with carbodiimide has not investigated yet. Another important factor that affects the development of regenerative templates is the scaffold porosity, which enhances the attachment, infiltration, and survival of cells within the scaffold. Several types of novel manufacturing techniques are being investigated to develop porous hydrogels and might be of great value in enhancing the regenerative potential of cellulose-based hydrogels [100–103].

7.7 Wound Dressings

To release people from pain, expressing wound dressing is a must during wound healing progression, and application of hydrogels in this field is a recent practice. Protecting the wound from infection is important particularly in cases of chronic wounds (e.g., ulcers), appropriate wound dressing is essential. In such cases, a moist environment encourages rapid healing, and hydrogels are suitable for the development of wound dressings, either as sheets or in amorphous form. Cross-linked amorphous hydrogels with low viscosity may be packaged in tubes or in foil packets to serve the purpose. The gels are reinforced with a gauze or a polymeric mesh to allow an easy removal and prevent gel liquefaction. Accurate moisture balance in the wound bed is necessary, and hydrogels should be designed to maintain moisture by

Table 1 Some commercially available hydrogel for wound dressings containing carboxymethyl cellulose (CMC) or sodium CMC (NaCMC) are given with producer company. These are mostly available in two forms, either as sheets or as amorphous gels. Products with silver ions show antimicrobial activity

Hydrogel wound dressing (producer)	Composition
IntraSite™ gel (Smith and Nephew)	Water Propylene glycol NaCMC
GranuGEL™ (ConvaTec)	Water NaCMC Propylene glycol Pectin
Purilon gel™ (ColoPlast)	Water CMC Calcium alginate
Aquacel Ag™ (ConvaTec)	NaCMC Silver ions (1.2%)
Silvercel™ (Johnson & Johnson)	Calcium alginate CMC Silver ions (8%)

hydrating the wound surface or absorbing the wound exudates. Hydrogels provide nonadherent dressings which result easy removal without any damage to the wound bed, and transparency of it is a further advantage in this application to monitor easily. A number of hydrogel dressings have been patented so far and are available in the market, based on synthetic or natural polymers or a combination of them. The recent patented hydrogels are in situ forming gels (e.g., based on sprayable formulations and consisting nanoparticles with antimicrobial agents and those of radiation cross-linked. In this regard, bacterial cellulose (BC) has been widely investigated for wound healing due to its purity and high water retention capacity, and they are available in the market. Some commercially available hydrogel dressing contains NaCMC, in combination with propylene glycol, which works as a humectant and a preservative (Table 1). It should be mentioned that the products developed are usually indicated for the treatment of specific wounds and often require the use of secondary dressings. Thus, currently a number of investigations have shown that the development of cellulose-based novel hydrogels cross-linked with hyaluronic acid for wound dressings with improved performance [75]. Wound dressing requires nontoxic, anti-allergic, transparent, and indicative for specified wounds which can be met by cellulose-based hydrogels, as in some cases cellulosic hydrogels give better options to the consumers than hydrogels from nonrenewable sources.

7.8 Plastic Surgery

As hydrogels resemble very close to body tissue, attempts were made to introduce hydrogels like new materials for plastic reconstruction (Fig. 6). In this case,

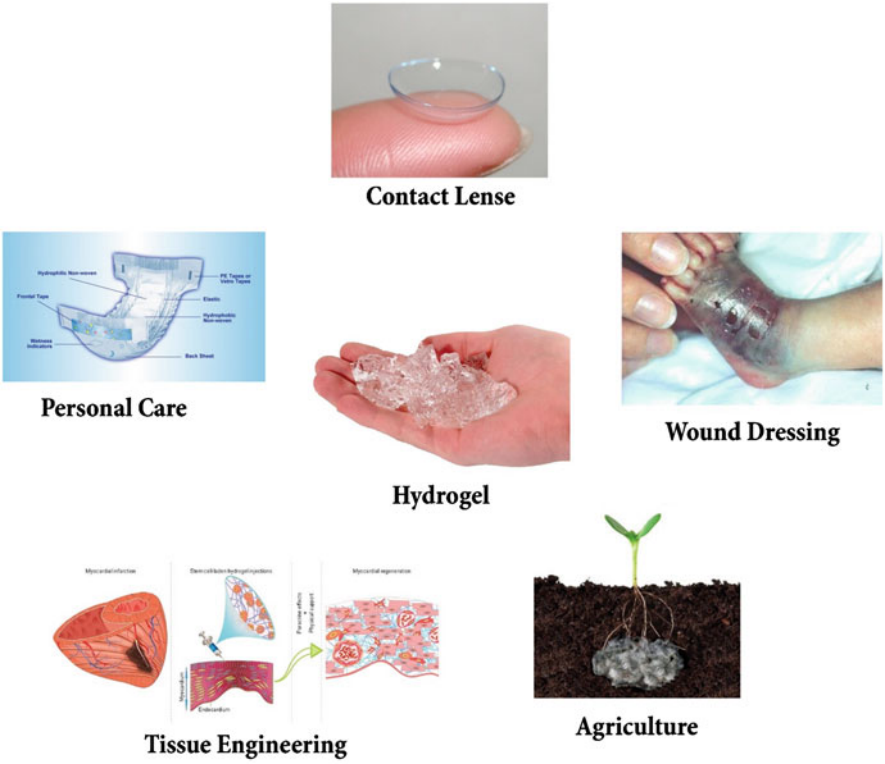

Fig. 6 Hydrogels in different forms of use

hyaluronic acid (HA) considered the panacea to resolve the problem as one notable company Macrolane^{TM} was using HA in tissue-filling applications to enhance breast size and shape and offer a more biocompatible alternative to standard and aggressive silicone prosthesis [104].

Hydrogel is such a field of research where multidisciplines have been involved and taking the fruit for the application of their own field.

8 Prospects of Cellulose-Based Hydrogels

Cellulose and cellulose derivatives are pioneer biocompatible materials for hydrogel synthesis. Compared to cellulose, other natural sources have scarcity all over the world, and in some cases, there is huge difference in costing. Again as much derivatives of cellulose have been practiced, but others from rest of the sources still remain unworked. Though synthetic hydrogels have better performance in some instances, non-biodegradation is the motivational factor for cellulose-based hydrogel research. Again synthesis of hybrid hydrogels through combination of some synthetic part with cellulose minimizes the property compromising

factor. Research have reached in such a position that cellulose-based hydrogels have gained almost same capability of absorbency and in some published article inform better performance than a synthetic one [48].

9 Conclusion

Hydrogel is an interesting and attractive research topic to the scientists for the last one decade. In this review, authors tried to give an idea of synthesis, application, characterization, and the development of cellulose-based hydrogels from simple polymeric network to smart materials. Another core objective was to establish cellulose and its derivatives as the eligible alternative for the protection of environment. To meet definite demand in applied field, many researchers have gained success in preparation of their hydrogel network. Biodegradability and biocompatibility are of the prime importance where there is no room for compromise. Petrochemical-based acrylic hydrogels are dominating due to some competitive reasons, but considering environmental sustainability hydrogels from biomaterials is drawing more attention to the researchers as well as consumers. Though cellulose-based hydrogels possess typically higher cost and less performance than the synthetic one and most of the volume of world production is consuming in hygienic uses, i.e., disposable diapers (as baby or adult diapers, feminine napkins, etc.), currently cellulose-based hydrogels are applying in numerous fields like contact lenses, hygiene products, wound dressing, biomedical, tissue engineering and drug delivery. Other than hygienic products, other commercial hydrogels are still limited. Much improvements have been made in the properties of hydrogels, but further improvements need to be made to improve the applicability of hydrogels. Though there are many patents on hydrogels, only a few reached in the market. In spite of the development of hydrogels, there are some drawbacks which should be overcome. Especially in hydrogels in drug delivery and tissue engineering, more progress is expected. Considering high cost and other hindrances, the necessity of preparation of renewable source-based hydrogels seems more obvious. The motivation for making greener world will show light to the researchers in the further development of hydrogels in the near future.

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Recent Advances of Multifunctional Cellulose-Based Hydrogels

2

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Abstract

Cellulose is an abundant and renewable natural resource with biodegradability and nontoxicity. Furthermore, cellulose and cellulose derivatives also have unique properties such as hydrophilicity, mechanical strength, biocompatibility, and tunable functionality due to the strong versatile hydrogen bonding. Cellulose-based hydrogels are prepared by physical or chemical cross-linking of cellulose derivatives with various functional molecules, which covalently bind different functional molecules and form a highly porous hydrogel, with three-dimensional network structure consisting of nanofibrillar-regenerated cellulose. Such cellulose-based hydrogels have great advantages due to high water-holding capacity, abundance, biodegradable biocompatibility and nontoxicity, which can be applied as superabsorbent in wastewater treatment (such as oil, heavy metals, dye, organic pollutants), as superabsorbent biomaterials, in pharmaceutical and biomedical field, in personal care and hygiene products, and tissue engineering and wound dressing. Moreover, they have also been used in catalysis, sensors, luminescence, and energy storage. This chapter will introduce the smart applications of cellulose-based hydrogels including native cellulose, cellulose derivatives, and cellulose-composite hydrogels. Among those, we will focus our discussion herein on the adsorption application of cellulose-based hydrogels. Most excellent research works are highlighted in this chapter, and cellulose-based hydrogels will be expected to be applied in agriculture, food, environment, industry, medical care, and personal health field. At last, we also give a prospect on cellulose-based hydrogels in the future.

Keywords

Cellulose-based · Hydrogel · Super-hydrophilic · Cross-linking · Superabsorbent

1 Introduction

Hydrogels are defined as cross-linking three-dimensional (3D) polymer networks filling great deal of water (or biological fluids) and mainly formed from biopolymers and/or polyelectrolytes [1]. According to the materials source, hydrogels can be classed into natural polymers and synthetic polymers. The polymer networks are formed as a result of the cross-linkers swelling in the aqueous solvent and retractive force exerted by the cross-linkers, until the elastic is totally able to neutralize the thermodynamic force of swelling [2]. This “solid-like solution” of polymer and water contained chemical or physical cross-linkers among the macromolecular

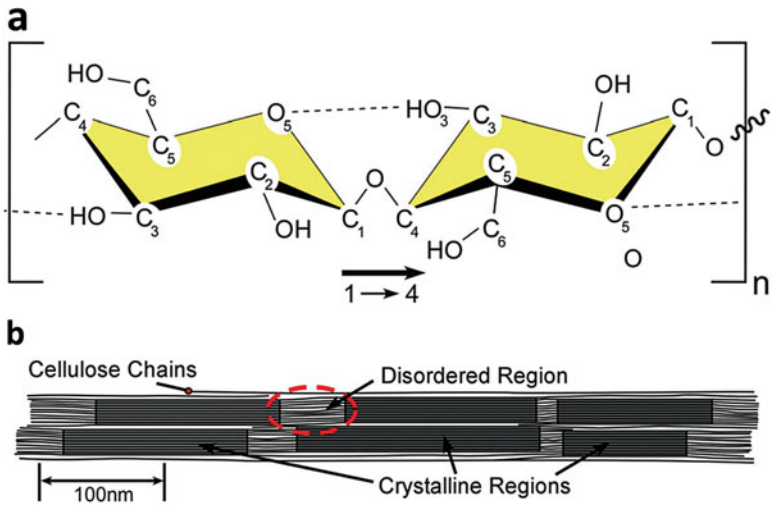

Fig. 1 (**a**) Repeating unit of cellulose, (**b**) the crystalline and amorphous regions of cellulose chains [11]

chains [3, 4]. Hydrogels could be synthetized by either physical method (including twine of chain, hydrogen bonds, van der Waals forces, and/or ionic interactions) or chemical method (covalent bonding). The 3D network is able to virtually prepare from any flexible polymers or semi-polymers and survive in several physical forms including papers, membranes, beads, microgels, microspheres, and nanoparticles, and even some hydrogels become cryogels or aerogels by directly drying or freeze-drying or supercritical drying, respectively [5–7].

A variety of hydrogels from natural polymers have been developed and showed potential application in biomaterials field because of their safety and nontoxicity [8, 9]. Cellulose is the most abundant reproducible resource on earth, meets the development of eco-friendly material, and will become the main material resource in the future [10]. Moreover, cellulose consisting of polymer of glucose (Fig. 1) was discovered as the main constituent of plants such as cotton and linen [11]. Some bacteria (*Acetobacter xylinum*) are also able to synthesize cellulose. Besides, microbial or bacterial cellulose (BC) has similar chemical properties with plant cellulose (PC) but impresses different macromolecular structure and physical properties [12]. The glucose units are bonded together by 1,4-β-glucosidic linkages among both BC and PC, leading to their insolubility in water and other common solvents, and the difference is crystallinity of cellulose (common in the range 40–60% of PC and greater than 60% of BC) [11]. In addition, numerous novel functional materials derived from cellulose are being developed over a diverse of applications, due to the increasing demand for hydrophilic, environmentally friendly, biodegradable, and biocompatible products [13, 14]. Cellulose hydrogels combine hierarchical micropore structures with the chemical nature of cellulose [15]. When blending with other functional materials, the resulted composites can combine desirable bulk properties

for the described one. So it is essential to study cellulose-based hydrogels in both fundamental research and industrial application [16].

Sol–gel technique is one of the most common synthetic processes used for the preparation of both polymer networks. In fact, native cellulose has poor solubility in water and other common solvent characteristic due to the inter- and intramolecular hydrogen bonds, so specific solvent systems are required to dissolve them [17]. The widely accepted view is that hydrogen bond connector (N-O, Cl-, OAc-, and so on) of the solvent breaks up the hydrogen bonds of macromolecule in the biopolymer chains under the mechanical or thermal treatment [18]. In this chapter, we review the physical hydrogels formed from native cellulose, cellulose derivatives, bacterial cellulose, and chemical hydrogels by chemical cross-linkers (including esterifying agents and etherifying agents). Cellulose that mixed with another polymer (natural polymer and synthetic polymer) or inorganics (metal nanoparticles, metallic compound, carbon materials) for novel gel materials with advantages of both components can be obtained. In addition, we elaborate some possible applications of cellulose-based hydrogels, which include water purification (such as dyes, heavy metal ions), water absorbents (personal care and hygiene, agriculture), biomedical applications (drug delivery, wound dressings, tissue engineering), and other applications (energy storage systems, catalysis, fluorescent light, templates).

2 Cellulose and Cellulose-Based Hydrogels

Cellulose is an abundant natural macromolecule and constructed by a polymer of glucose, commonly produced from plants and natural fibers or bacteria. Hydrogels are three-dimensional networks expanding with great amounts of solvent and cross-linked by physical interactions (such as hydrogen bonds, hydrophobic interactions, electronic interactions, van der Waals forces) or chemical actions (covalent bonds). For physical interactions, cellulose hydrogels are mainly synthesized from four sources: native cellulose (dissolved in appropriate solvents, such as polar solvents, ionic liquids, and alkali/urea), cellulose derivatives (dissolved in water or acid), bacterial cellulose (BC, also dissolved in specific solvents like native cellulose, or biosynthesized directly into gels). For chemical actions, they have been mainly prepared through the chemical cross-linkers, small bifunctional or multifunctional molecules. The cross-linkers can be classed into two types, agents with esterification including carboxylic acids and carboxylic anhydrides and agents with etherification including organochlorine, epoxide, and vinyl compounds. In fact, there are massive hydrogels mixed with another polymer or inorganics to obtain multifunctional hydrogels for versatile applications.

2.1 Hydrogels from Native Cellulose and Cellulose Derivatives

Cellulose hydrogels can be directly fabricated from cellulose solutions due to many hydroxyl groups forming hydrogen bonding and linking networks. However, the

existence of highly swollen hydrogen-bonded structure also makes cellulose lacking specific solvents to dissolve [19]. To date, a few of solvents have been developed to dissolve native cellulose, such as polar solvents like lithium chloride/dimethylacetamide (LiCl/DMAc), *N*-methylmorpholine-*N*-oxide (NMMO), ionic liquids (ILs), and alkali/urea. The exploration of LiCl/DMAc as solvent started the development of native cellulose hydrogel production. Glasser et al. fabricated cellulosic hydrogel as bead forms through dropwise cellulose into LiCl/DMAc solution to azeotropic methanol or isopropanol as non-solvent system [20]. The LiCl/DMAc solution can be used to dissolve cellulose polymers with a weight range (from degree of polymerization, DP 100–4000). In addition, a battery of the polar solvent systems such as LiCl/DMAc for cellulose powder (0.5–8 wt%), paraformaldehyde (PF)/dimethyl sulfoxide (DMSO) for cellulose pulp (4 wt%), and triethylammonium chloride (TEAC)/DMSO for the wood pulp (0.5–1 wt%) have been applied [21–23]. NMMO solution provides a simple viscose technology for preparing cellulose products. Zhang et al. manufactured cellulose gels by dissolving cotton pulp (7-11 wt%) with NMMO under stirring and heating at 85 °C and found that the cellulose concentration is a determining factor [24]. However, there are few transparent hydrogels synthetized from the native cellulose solution with a NMMO system. Some hydrophilic ionic liquids can also dissolve cellulose. Li et al. used 1-allyl-3-methylimidazolium chloride as solution and water as coagulant to prepare cellulose hydrogels [25], while Kadokawa et al. reported 1-butyl-3-methylimidazolium chloride dissolving cellulose for gels [26]. The cellulose products are obtained from ionic liquids by following addition of water, alcohols, or ketones, presenting the same DP as the initial cellulose. Recently, alkali and alkali/(thio)urea system have been alternatives for cellulose solution. Zhang et al. prepared 7 wt% NaOH/12 wt% urea aqueous and precooled below −10 °C; the cellulose could dissolved rapidly and be adjusted by changing the cellulose content and the post-treatment (Fig. 2a–d) [27]. They also reported a NaOH/thiourea aqueous system by employing a pre-gelation processing [28].

Cellulose presents as random nanofibers, semirigid chains, and/or tangled chains in these solutions, with the degree of crimp lying on the cellulose concentration [29, 30]. The cellulose is completely isotropic when its solution is in low concentration, and a solution to a liquid crystalline gel takes place with the increase of the solution concentration, and then gelation forms solid hydrogels which have a twine structure [31]. Physical interactions are common reversible progress, with a thermo-reversible and "green" sol–gel transformation. The transparency property of hydrogels is defined as their ability to transmit light. The transparency of hydrogel is diverse and varies with the processing temperature or coagulation bath during the gelation. This parameter is caused by the degree of phase separation (or spinodal decomposition, where liquids or solids form one thermodynamic phase to two coexisting phases) [21, 32]. In majority of situation, higher strength means higher transparency and similarly lies on the degree of phase separation. Moreover, employing a pre-gelation process before the coagulation bath can improve the mechanical strength of native cellulose hydrogels. The most common cellulose derivatives are hydrophobic modified cellulose. The derivatives became water

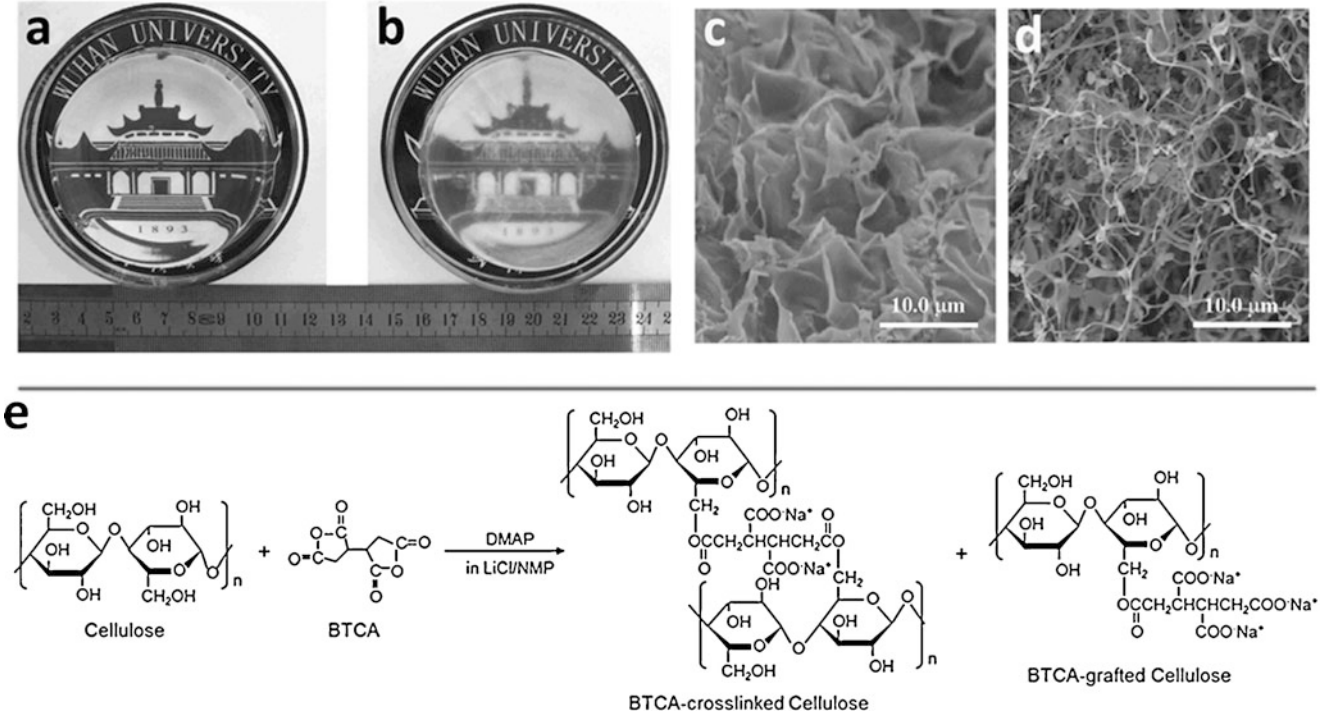

Fig. 2 Photographs and SEM images of the cellulose hydrogels prepared by heating and freezing methods in NaOH/urea: (**a**) and (**c**) heated hydrogels, (**b**) and (**d**) frozen hydrogels [27], (**e**) reaction of chemical cross-linking (1,2,3,4-butanetetracarboxylic dianhydride) and cellulose for gels [45]

soluble as a result of the introduction of pendant groups and can form hydrogels more easily [33]. By hydrophobic or electrostatic associations, these derivatives could be prepared to thermoset and pH-sensitive hydrogels [34]. For an example of these gels, elastic and thermo-reversible hydrogels were obtained above a critical temperature through heating the modifying cellulose aqueous solution. The mechanism of this gelation is solvent reorganization during heating process of the solution, where the solvated 3D framework structure (formed through hydrogen bonds) is destroyed that leads to the exposure of hydrophobic regions of modified cellulose, therefore forming the hydrophobic aggregates [35].

2.2 Bacterial Cellulose (BC) Hydrogels

Bacterial cellulose prepared from microbial strains is generally called *Acetobacter xylinum* with an ultrafine network structure [14]. BC has quite different properties from plant cellulose, including high tensile strength and modulus, high moldability, high hydrophilicity, and high biocompatibility [36]. During gel layer formation, first a gel pellicle emerges on the surface, and its thickness enhances steadily with time increasing [37]. On the basis of such superior properties, BC hydrogels have been applied in a broad range of the biomaterials fields. These BC hydrogels helped the aerobic cells of bacterial cellulose to keep their position near the oxygen-rich surface and protect themselves from sterilizing under extreme conditions including dehydration, ultraviolet lights, and heavy metal ions [38].

Gelin et al. have investigated the effect of the water present in as-synthesized BC gels by dielectric spectroscopy [39]. The results indicated that only about 10% of water molecules in BC gels behaved like free bulk water, and the majority in the gels are more or less tightly bound to the cellulose. Putra et al. used proper fibril orientation to fabricate a tubular BC gel [40]. Here, BC gels can be easily formed into desired shapes and sizes due to their inappropriate orientation at the air/liquid interface. They found desired length, inner diameter, and thickness with uniaxially oriented fibrils could be produced from culturing BC in oxygen-permeable silicone tubes (BC–TS gel) (<8 mm).

2.3 Hydrogels with Chemical Cross-Linkers

However, gels from pure cellulose solution with physical interactions express weak after heating or storage for a long time. To ensure the stable structure of cellulose hydrogels, it is significant to develop a covalently bound 3D network during gelation. Small bifunctional or multifunctional molecules are the widely used chemical cross-linkers. Such linkers can be divided into two categories in accordance with the mechanism: one is esterification of cross-linkers including carboxylic acids and carboxylic anhydrides, resulting in formation of -COOR bonds; another is etherification of cross-linkers including organochlorine, epoxide, and vinyl compounds, resulting in formation of R-O-R bonds.

Sannino et al. prepared superabsorbent hydrogels by using divinylsulfone (DVS) as cross-linker to connect carboxymethyl cellulose [41]. Hirsch et al. explored mechanical properties and swelling capacities at different cross-linking temperatures; the as-synthetized gels swelled at lower temperatures while contracted at higher temperatures [42]. Marsano et al. synthesized thermally sensitive hydrogels by cross-linking hydroxypropyl cellulose (HPC) with poly(ethylene glycol) diglycidyl ether [43]. Yan et al. reported a hydrogel cross-linked by HPC with epichlorohydrin (ECH) exhibited an excellent ability in adsorption of anionic dye [44]. However, both DVS and ECH are toxic reagents, so they must be effectively removed after the hydrogels are produced. In general, not only the degree of spinodal phase separation affected transparency of chemical hydrogels compared to physical hydrogels, but the extent of cross-linking also has an effect. Kono et al. fabricated superabsorbent cellulose hydrogels by esterification cross-linkers with 1,2,3,4-butanetetracarboxylic dianhydride (BTCA) under mild conditions (Fig. 2e) [45]. Chemical cross-linker contributes to a highly hydrophilic 3D network with a homogeneous structure. The initial pore size of the hydrogels is dependent on the preparation process, for example, when the process temperature is above the lower critical solution temperature, the hydrogels are microporous. The mechanical strength of chemical hydrogels is dependent on biopolymer concentration and cross-linkers' density; the stress increased with the concentration and density.

Irradiation is an advanced method for achieving chemical hydrogels, including irradiation of solid polymer, monomer, or polymer aqueous solution [46]. Such radical cross-linkers lead to a higher purity of the hydrogel product due to their nontoxicity. Radiation cross-linker of carboxymethyl cellulose (CMC) with a diverse degree of substitution (DS) was investigated by Fei et al.; they found that a high DS and a high concentration in an aqueous solution were effective to form cross-linkers of CMC [47]. Liu et al. prepared hydrogels by using radiation-cross-linked CMC-Na as a substitute by gamma irradiation below gelation dose; such gels can be used at room temperature and produced at low dose [48]. Wach et al. fabricated HPC hydrogel by electron beam irradiation, which gave higher gelation up to 90% than gamma irradiation [49]. Electron beam (EB) technique has revealed that the process is dependent on concentration. Both electron beam and gamma-ray processes, used to degradation and cross-linking, take place at high-energy irradiation of cellulose derivatives with either.

2.4 Cellulose-Polymer Composite Hydrogels

In fact, most of the pure cellulose hydrogels could not be applied in some specific usage as a result of the lack of appropriate structure or property. Novel hybrid hydrogel materials can be obtained with the advantages of both components through blending with other polymers or inorganics, which enormously improve the performance of the as-prepared composite hydrogels in various fields. It is an extremely attractive choice by mixing different polymers, providing an extremely inexpensive route and advantage to obtain new hydrogels. Zhou et al. synthetized biodegradable

cellulose/chitin gels in 6 wt% NaOH/5 wt% thiourea aqueous solution, which showed a high adsorption ability to heavy metals [50]. The hydrophilic framework and micropores of cellulose improve the adsorption ability of chitin. Li et al. reported a chitosan–cellulose hydrogel cross-linked with ethylene glycol diglycidyl ether, which improved the chemical stability of gels at low pH [51]. Tang et al. fabricated chitosan/methylcellulose hydrogels with the addition of salts including NaCl, Na_3PO_4, $NaHCO_3$, and glycerophosphate (GP); which processing temperature followed the order NaCl > GP > Na_3PO_4 > $NaHCO_3$, gels rate followed the order GP > $NaHCO_3$ > Na_3PO_4, and strength of gels followed the order GP > $NaHCO_3$ > Na_3PO_4 (at 37 °C) [52]. Baumann et al. prepared a series of physical hybrid hydrogel composed of hyaluronan and methyl cellulose, which displayed the advantages in design criteria of injectability and safe swelling [53]. Rao et al. developed a NaAlg/hydroxy ethyl cellulose hydrogel by precipitating the viscous blend solution in alcohol and cross-linking with calcium chloride, and the ability of controlling the release of diclofenac drugs has been investigated [54]. Chang et al. prepared cellulose/sodium alginate macroporous hydrogels by cross-linking with epichlorohydrin and characterize the structure, morphology, gelation conditions, strength, and equilibrium swelling ratio [55].

Polyvinyl alcohol (PVA) is a good alternative cross-link network for the preparation of hydrogels through diverse technologies such as chemical bonding, electron beam, and physical linking. Abitbol et al. reported PVA/cellulose hydrogels by cyclic freezing and thawing (Fig. 3a–f); the confined compression and the elastic moduli of hybrid gels have been enhanced relative to pure hydrogels [56]. Zhang et al. further investigated the structure and properties of cellulose/PVA gels with the effect of cross-linking; all as-prepared gels exhibited homogeneous porous structures and a certain miscibility [57]. Taleb et al. fabricated PVA/carboxymethyl cellulose gels using electron beam irradiation as a cross-linking agent, and they studied the thermal behavior and swelling properties of composite hydrogels [58]. Polyvinylamine (PVAm) is commercially available, containing a series of copolymers such as poly(*N*-vinylformamide) (PNVF), which could be applied as cationic polymers to prepare carboxymethyl cellulose, PVAm/carboxymethyl cellulose, and PVAm-co-PNVF/carboxymethyl cellulose hybrid with macroscopic, homogeneous, and transparent properties. Feng et al., respectively, prepared carboxymethyl cellulose/pure PVAm and carboxymethyl cellulose/PNVF gels and measured the tensile strength and tensile modulus with the effect of polymer ratio, molecular weight, and water content [59].

Two or more polymers blending into one network are defined as interpenetrating polymer networks (IPNs). IPNs in the context of cellulose-based hydrogels could be classed into two types, sequential IPN and semi-IPN, which the cellulose is conducted as the first network and polymerizing in the presence of the cellulose network is used as second network; such mixture networks can be called as sequential IPN. For the semi-IPN, hydrogel formed from cellulose or its derivative is linear or branched with a cross-linking network. Gelatin gels are easily broken into fragments under a modest compression; Nakayama et al. synthesized double-network hydrogels with high-mechanical-strength combined polymers BC with gelatin [60].

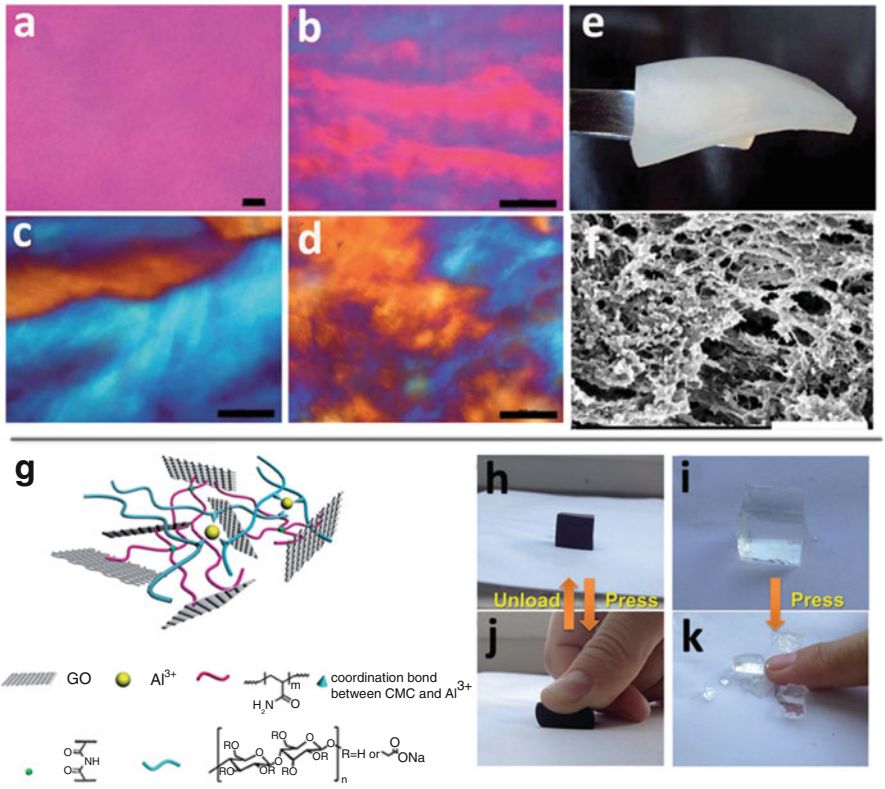

Fig. 3 (**a**–**d**) Polarized optical micrographs of different cellulose loading hydrogels, (**e**) and (**f**) photographs and SEM images of PVA/cellulose hybrid hydrogels [56], (**g**) schematic diagram of GO/PAM/CMC ternary nanocomposite hydrogels, (**h**–**k**) photographs of GO/PAM/CMC and PAM/CMC hydrogels under pressure [71]

Buyanov et al. prepared hybrid gels through synthesis of PAAm networks into the BC matrices; the hydrogels displayed excellent mechanical properties (such as compression strength up to 10 MPa) [61]. Caykara et al. reported a linear HPC and cross-linked P(NTBA-*co*-AAm) hydrogels by the semi-IPN technique; such semi-IPN hydrogels underwent a volume phase transition between 18 °C and 22 °C as a function of the amounts of MBAAm and HPC [62].

2.5 Cellulose-Inorganic Hybrid Hydrogels

In recent years, introduction of inorganic into cellulose hydrogel is a creative way to prepare materials with highly effective functionality and has attracted increasing attention in diverse fields. Simply mixing the target inorganics with the cellulose solution and then shaping into a gel is a rapid and effective approach. Chang et al.

fabricated cellulose and quantum dot (CdSe/ZnS) hydrogels in a NaOH/urea aqueous system via a mild chemical process [63]. The cellulose/quantum dot hydrogels showed strong photoluminescence (PL) emission and nearly pure color depending on the size of the QDs. By introducing inorganic target from inorganic precursor into the cellulose solution (or suspension) along with (or followed by) gelation is also an advanced technique to fabricate cellulose-inorganic hybrid hydrogels. Sequeira et al. synthesized cellulose/silica hybrid using eucalyptus-bleached kraft pulp as the cellulose source and tetraethyl orthosilicate (TEOS) as the silica precursor and the heteropoly acids (HPAs) as catalysts by a sol–gel method [64]. Bagheri et al. developed cellulose-ZnO gels through the dissolution of cellulose with microwave assisted in ionic liquid 1-butyl-3-methylimidazolium chloride and then added premixture of $Zn(CH_3COO)_2{\cdot}2H_2O$ and NaOH [65]. The as-prepared gels have a catalyst behavior due to zinc oxide nanoparticles in the cellulose matrix.

In situ transition of the precursor in the cellulose gel takes advantage of guaranteeing the structural integrity of gel networks and has attracted a great attention. Wu et al. synthesized Ag nanoparticles decorated by an eco-friendly hydrothermal process on porous cellulose with a sol–gel transition processing; the hybrid exhibited good catalytic activity [66]. Luo et al. prepared regenerated cellulose microspheres followed by in situ synthesis of Fe_3O_4 nanoparticles into the gels and created the magnetic-induced transference [67]. Ashori et al. immersed BC hydrogels into an aqueous solution of tetraethoxysilane (TEOS), followed by pressing the disposed BC matrices (at 120 °C and 2 MPa) for obtaining water-free translucent blended gels [68]. While Katepetch et al. synthesized and simultaneously incorporated ZnO into 3D BC networks by ultrasonic-assisted in situ synthesis [69]. Hutchens et al. applied calcium-deficient hydroxyapatite (CdHAP) deposited in a natural BC hydrogel, exhibiting potential application in an orthopedic biomaterial [70]. The fermentation of BC as a template for the ordered support of target inorganics is a biosynthesized technology according with ecological economy. Graphene oxide (GO) has inspired great interests for nano-reinforcement of polymer because of its high special surface area. Zhang et al. prepared GO/polyacrylamide (PAM)/carboxymethyl cellulose sodium hydrogel with superior mechanical strength and good swelling behavior (Fig. 3g–k) [71].

3 Applications of Cellulose and Cellulose-Based Hydrogels

Cellulose and cellulose-based materials are fascinating hydrogel precursor, as a result of their low cost, large availability and regeneration, and environment-friendly abilities. In most cases, such glamorous biodegradability of hydrogel is required or recommended to various applications. This section reviews some possible applications of cellulose-based hydrogels; these applications are attributed to macroporous structure, hydrophilicity, and biocompatibility of cellulose-based hydrogels such as water purification, water reservoirs for agriculture or personal care and hygiene, drug delivery, wound dressings, tissue engineering, and other applications.

3.1 Water Purification

Water pollutions have not only brought about severe environmental problems but also threaten people's health and the sustainable development of economy. The wastewater is commonly complex with diverse pollutions, such as oil, organic pollutants, heavy metal ions, and dye contamination [72]. A large number of liquid- and/or solid-phase extraction techniques have been implemented for the purification of pollutants from water including chemical precipitation, burning, mechanical collection, membrane filtration, ion exchange, and electrochemical catalysis [73–75]. Hydrogels, which exhibit high adsorption ability due to porous structure, abundant functional groups, and relatively low density after drying, have achieved particular attention for pollution removal from water, especially cellulose-based hydrogels with biodegradability, biocompatibility, and nontoxicity. Besides, decoration of another component into the hydrogel matrix entrusts the resulting hybrid networks with abilities to remove different aquatic pollutants.

Heavy metal ions are highly toxic even at low concentrations and can accumulate in vivo leading to body disorders and diseases. Therefore, it is extremely urgent to reduce or clear up the heavy metals from industrial sewage diffusing into the environment. For an adsorbent, the adsorption efficiency often depends on its specific surface area and surface functional groups [76, 77]. Blending two or more polymers has become a charming technique for the investment of novel biomaterials, which exhibits advantages of combinations that could not be available by the single polymer. Zhou et al. prepared carboxylated cellulose/chitosan hydrogel which exhibits an adsorption capacity of 171.0 mg g^{-1}, and the carboxylate groups on the carboxylated cellulose surface played key role in Pb(II) adsorption [78]. Liu et al. prepared Fe_3O_4 coated cellulose–chitosan hydrogels as reusable adsorbent for heavy metal ions; it greatly enhanced the stability of nanoparticles through preventing their aggregation and oxidation and made recycling more convenient (Fig. 4a–b). Moreover, it also showed high absorbency with the abundant amino and hydroxyl functional groups from polymers [79]. Isobe et al. introduced nitroxyl radical-catalyzed oxidation with hypochlorite/bromide (TEMPO oxidation) oxidation onto the surface of the cellulose hydrogel; the TEMPO oxidation carboxyl groups onto the surface of the cellulose hydrogel and the hybrid displayed high adsorption capacity for diverse toxic metal ions such as Zn^{2+}, Fe^{3+}, Cd^{2+}, and Cs^{+} [80].

Dyes are widely used for different purposes such as in textile, tannery, printing, cosmetic, and petroleum. These dye molecules or their metabolites are hard to biodegrade under natural conditions and thus may be potentially hazardous to living organisms [81]. Activated carbon is used in common adsorption technique due to its effectivity and inexpensive. Cellulose-based hydrogels are the effective potential adsorbent for the removal of toxic dyes due to their advantages of low-cost, nontoxic, synergistic effect between the nanosize and polymer matrix and excellent mechanical, higher surface area and hydrodynamic radius. Pei et al. fabricated quaternized cellulose gels, and it exhibited dye adsorption capacity of 0.95 mol kg^{-1} for Congo red and 1.10 mol kg^{-1} for acid green 25 because of their high specific surface area and surface cationic charge density. Besides, the cellulose could also

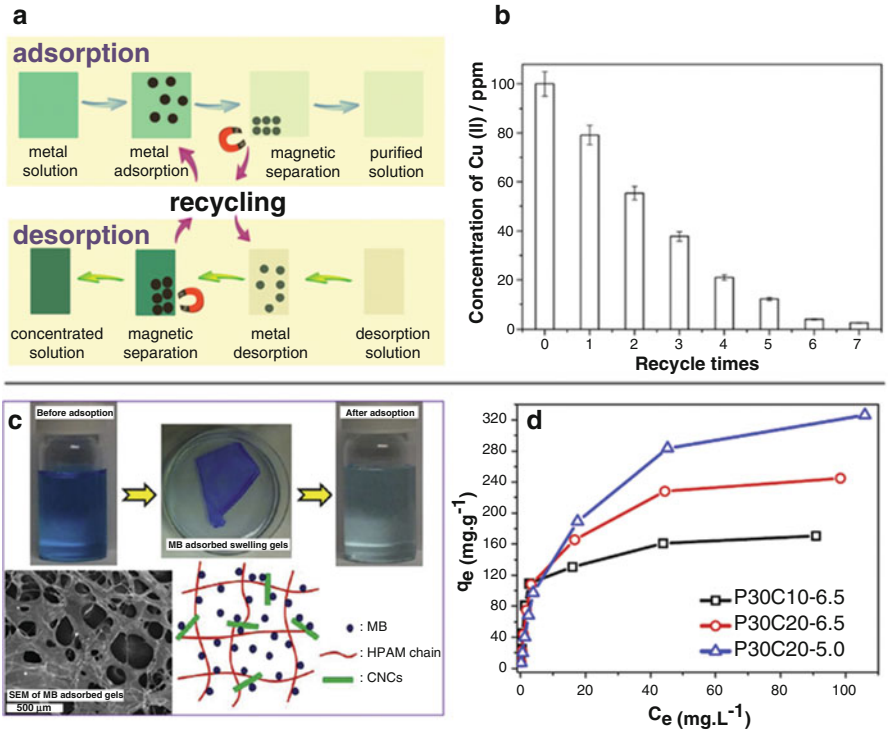

Fig. 4 (**a**) Overall process of adsorption and desorption of heavy metal ions, (**b**) recycling times as a result of the concentration of Cu^{2+} [79], (**c**) scheme of the MB adsorption behavior of nanocomposite hydrogels, (**d**) adsorption isotherms of MB on diverse hydrogels. P30C10-6.5 represents a gel comprised of 90 wt% of HPAM with 30% of anionicity and 10 wt% of CNCs [83]

high-efficiently remove cationic and anionic dyes [82]. Zhou et al. obtained hydrolyzed polyacrylamide (HPAM)/cellulose nanocrystal (CNC) hydrogels by a simple thermal treatment, which exhibited maximum methylene blue adsorption about 326.08 mg g^{-1} (Fig. 4c–d) [83]. Liu et al. prepared cellulose-based hydrogels by grafted acrylic acid and acrylamide; such hydrogels could remove anionic dye acid blue 93 (AB93) and cationic dye methylene blue (MB) from single and binary dye solutions [84]. The maximum adsorption capacities of hydrogels were 1372 mg g^{-1} for AB93 and MB.

3.2 Superabsorbent Cellulose-Based Hydrogels

3.2.1 Superabsorbent for Personal Care and Hygiene

Biocompatibility superabsorbent hydrogels can absorb fluids and keep moisture and humidity away from the skin in order to improve health and comfort of consumer [85, 86]. However, conventional superabsorbents like acrylate-based

hydrogels are currently extensive and sophisticated. There is an estimation that thousands of hospitals and group care centers in the majority of countries employ disposable diapers containing a superabsorbent polymer. Moreover, demand trends of such products in training pants and adult incontinence have been raising worldwide. Research have reported a great deal of documents that elaborate the advantages of using superabsorbent materials in personal care and hygiene including safety and effectiveness [87, 88]. The superabsorbent not only prevents the diaper rash caused by dry skin but also controls the spread of germs, which is significant in decreasing the risk of derelict contamination and reducing the potential for the spread of illness in care centers. Adalat et al. studied the incidence and prevalence of diaper dermatitis that varies in detail; they found disposable diapers that were crucial to decrease risks of spreading gastrointestinal illnesses [88].

In 1982, superabsorbent was first used in the diaper fields and was only introduced by Unicharm in Japan and followed by application in sanitary napkins. After that, different attempts have been carried in diverse personal care and hygiene including disposable diapers, napkins, hospital bed sheets, and sanitary towels [89]. In majority of cases applied in superabsorbent, the cellulose exhibited the similar structure: they contain non-woven tissue as a wrappage, plastic material as a cover, and fluff of wood pulp cellulose as an absorbent. Recycle diaper must be separately collected to recover the biodegradable fraction of cellulose and the other portion including acrylate-based hydrogels which are not biodegradable but also could be recycled for other uses [90]. Recently, the cellulose-based hydrogels have been developed as a substitute to deal with the problem of recycling of superabsorbent; thus the recycle diaper is totally biodegradable. Sannino et al. prepared novel hydrogels based on cellulose derivatives including sodium carboxymethyl cellulose and hydroxyethyl cellulose chemically cross-linked with divinylsulfone, which exhibited superior swelling capabilities than those displayed by superabsorbent and high water retention capacities after centrifugal loads [91]. Cellulose-based hydrogels used as superabsorbent take the main advantage of their biodegradability and environmentally friendly nature. Demitri et al. synthetized new cellulose-derived eco-friendly hydrogels, and such superabsorbent hydrogels showed excellent biodegradable properties [92]. Moreover, swelling properties have been adjusted performing on the degree of cross-linkers of the polymer networks, and the hydrogel biocompatibility has been investigated according to its capability either to guide nitric oxide and lactate dehydrogenase release by macrophages or affect viability of macrophages. The biocompatibility is consistent with the hypothesis and displays a high level of biocompatible ability which indicate this gel may be an alternative to diuretic therapies in special pathologic conditions. Esposito et al. prepared an orally administered cellulose-polyethyleneglycol gel; the gel demonstrated their high water-sorption properties (Fig. 5a), and biocompatibility studies showed that the hydrogel would not influence negatively cell viability (Fig. 5b), which indicated the obtained hydrogel could serve as a potential treatment for intractable edemas [93].

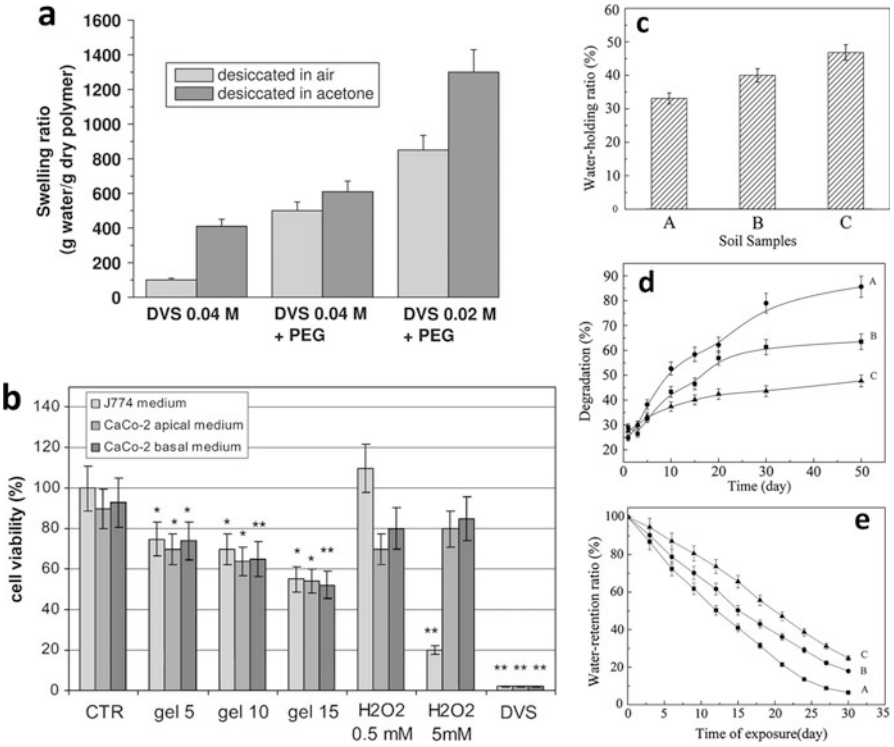

Fig. 5 (**a**) Hydrogel equilibrium swelling ratio in distilled water, (**b**) cell viability measured by contacting with the gel or with CaCo-2-conditioned medium of cellulose-PEG hydrogels [93], (**c**) and (**e**) largest water-holding ratio and water retention behaviors of different soil samples (A, pure soil; B, 1 g coated CRF; C, 2 g coated CRF), (**d**) degradation of P(AA-AMPS-NHMAAm)/WS superabsorbents [99]

3.2.2 Water Reservoirs in Agriculture

Agriculture and horticulture require decreased water consumption and manage water resources. Superabsorbent hydrogels have achieved increasing interest and deserved the attention of both academic and industrial research in agriculture [94]. The hydrogels play an important role in the enhancement of newly human habit toward water, which to be considered as a benefit to save and not as a surplus to waste. It is known that the hydrogels have a translation from the glassy to the rubberlike state during swelling process; meanwhile they could store large amounts of water even under compression [95]. In addition, the swollen hydrogel is able to slowly release water when in the interior and the outside of the material exists a gradient of humidity. Water molecules, loaded in the polymer skeletons along with the synthesis of hydrogels, can be released through a controlled and sustained management with diffusion method. Xerogel (dry hydrogel), which exists in the form of powder or granules, is introduced for the purpose of planting by envisaging to be blended with

the clay in arid and desert regions, where there are absolute scarcity of water sources and lacking of flora. As the hydrogel absorbed the water or nutrients followed by cultivation, they release water and nutrients to the soil when required following diffusion-driven mechanism, thus guaranteeing the sufficient moisture for plants over a long period. Another advantage of using hydrogels is connected with the effect of the swelling, hydrogel granules has fine dimensions before swelling as well as the substrate granules, and they promote the dimension after adsorbing water to enhance the porosity and support a better oxygenation to the plant roots.

A few of commercial product absorbents, retaining and releasing water, have been applied in this field and exhibit their good efficiency in saving water [96]. However, their water retention capacities are extremely high and hard in management, presenting the risk for cultivations. For cellulose-based hydrogels, the cellulose is a renewable natural resource with biodegradability and nontoxicity and fits perfectly as superabsorbent in the agriculture to replace the acrylate-based hydrogels. Sannino et al. reported a series of absolutely biodegradable and biocompatible 3D cellulose-based hydrogels with numbers of micropores served as superabsorbent [97]. Such hydrogels were able to absorb up to 1 L water per gram of dry material, without releasing it even under compression. The hydrogels could be prepared both as the type of a powder and a bulky material with a well-defined shape and a superior shape memory after swelling. While mixed with small molecules such as nutrients, the hydrogels could be released under a controlled kinetic in agriculture. The soil with the addition of hydrogels remained humid for four times longer than those of pure soil. Marcì et al. prepared cellulose hydrogels as non-petrochemical reserves and renewable superabsorbent [98]. Paradoxically, a small difunctional molecule divinylsulfone (DVS), used as a cross-linker for the hydrogel, was highly toxic. The toxic agent was efficiently removed along with the unreacted polymers and irradiated by the environmentally sustainable heterogeneous TiO_2 with photo-catalyzed process. The treated hydrogels as newly superabsorbent showed tendency of water retention in the agriculture. However, it is necessary for carrying out experimental greenhouse on the spot where the paucity of water has been a common problem. Xie et al. prepared coated controlled-release fertilizer (CRF) based on wheat straw; the CRF granules indicted high water-holding abilities and good degradation properties in soil solution (Fig. 5c–d), which could be promising for applications in agriculture and horticulture [99].

3.3 Biomedicine Application of Cellulose-Based Hydrogels

3.3.1 Drug Delivery

Cellulose allows a drug release derived from swelling as physiological fluids and is involved in contacting with the tablet itself while being used in solid tablets [100]. It starts to swell on the tablet surface and is transformed into a physical hydrogel with chain entanglements and followed by the drug that gradually dissolves in water and diffuses out from the hydrogel network. Thus drug release was a complex process with combination of swelling, diffusion, and erosion [101].

Incorporating another component into the hydrogels with diverse dosages would obtain different structures and morphologies in the 3D network, therefore governing their diffusion properties. Chang et al. prepared hydrogels from carboxymethylcellulose (CMC) sodium and cellulose cross-linking with epichlorohydrin in the NaOH/urea aqueous [101]. As-synthetized hydrogels displayed smart swelling and constriction in NaCl or $CaCl_2$ aqueous solution; besides, managing CMC portion could control the release of bovine serum albumin (BSA, Fig. 6a–f). Lignin, as another biopolymer developed by Ciolacu et al., also resulted in a more homogenous and less

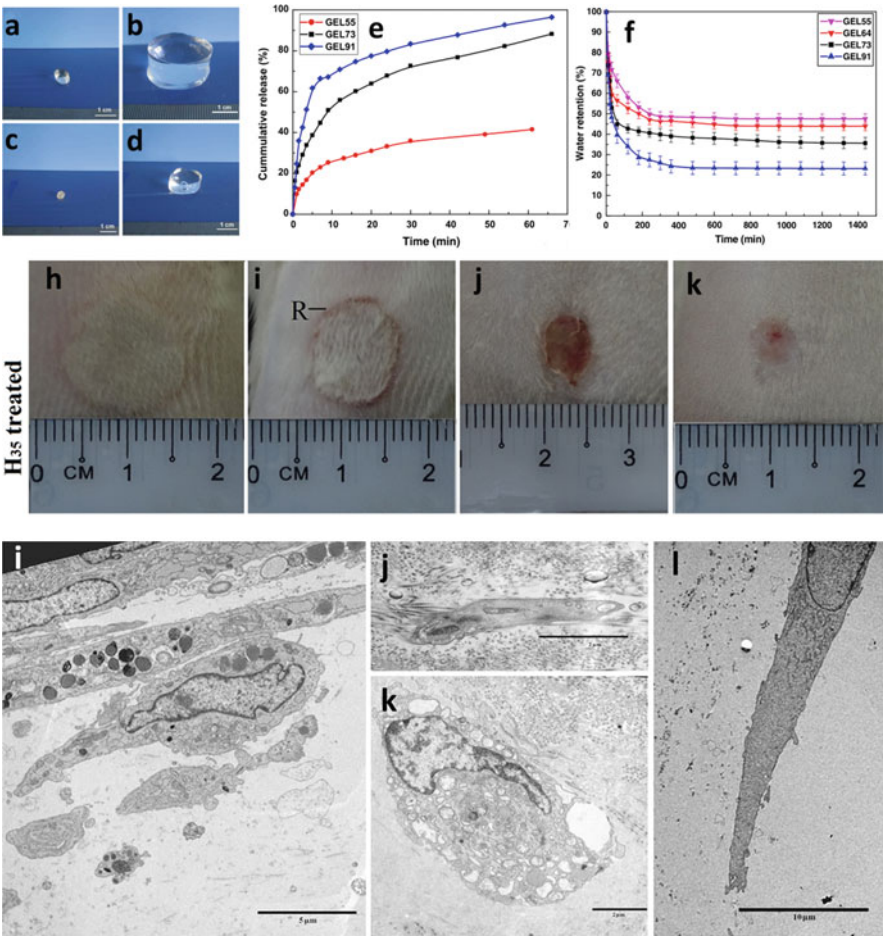

Fig. 6 Photographs of original hydrogel and swollen hydrogel (**a**–**b**) in water and (**c**–**d**) in NaCl solution; (**e**) deswelling kinetics of cellulose/CMC hydrogels in 0.1 M NaCl solution at 37 °C; (**f**) percent cumulative release of BSA in vitro [101]; (**h**–**k**) photographs of wounds treated with hydrogels by electron beam irradiation at doses of 35 kGy ($H_{3.5}$) after days 1, 3, 7, and 14 [115]; morphology of human chondrocytes grown in (**i**) native BC; (**j**) articular cartilage surface; and (**k**) articular cartilage bulk, ingrowth of human chondrocytes in native BC [124]

dense structure and an increase in the release rate as a result of an addition of lignin content [102]. These revealed that the higher density and smaller pores contribute to a reinforcing structure and a slow release rate. Wang et al. reported cellulose/poly (*N*-isopropylacrylamide) hydrogels by controlling the content of MBAAm to adjust the swelling ratio of hydrogels [103]. Dimethyl methylene blue was used as a model drug to examine the loading and releasing performances of the hydrogels. Besides, hydrogels that can reversibly change in response to environmental condition can also manage drug release. The most commonly researched type of environmentally sensitive systems is temperature-sensitive hydrogels in drug delivery field. Sanna et al. developed thermo-responsive poly(*N*-vinylcaprolactam)/nanocrystalline cellulose hydrogels; the gels displayed a decreased swelling ratio along with increased temperature and therefore could be used as "on–off" release devices [104].

All efforts are deserving if drug release could be adjusted in a manner that precisely fits the physiological requirements at specific sites (site-specific targeting). Controlling pH triggering is an attractive and the most common route of targeted release. The pH gradient in the human intestines and stomach impresses different values (stomach 1–3, saliva 5–6, colon 6.4–7.0, and intestine 6.6–7.5) [105]. Amin et al. fabricated pH-responsive BC/acrylic acid hydrogels for drug delivery; the hydrogel systems showed minor swelling at acidic pH and large swelling around neutral pH, which can be applied in intestine or colon-specific delivery [105]. Pandey et al. grafted polymerization of acrylamide on BC as superabsorbent smart-swelling hydrogels; the hydrogels exhibited higher porosity, drug loading, and releasing efficiency for oral drug delivery contrasted to the hydrogels synthesized using dispersed BC [106]. Thermoset hydrogel systems are able to be injected into the body directly as a liquid and in situ transform in the form of a gel, while their critical solution temperature is below the body temperature and has the potential to act as targeted drug carriers without requiring invasive surgeries. In addition, such hydrogels could comparatively prolong the release time reaching a few weeks because of the efficient encapsulation of drugs. Luo et al. reported Fe_3O_4/cellulose gels by in situ synthesized route; the prepared microspheres perform a key role in both the formation of the magnetic transference and the improvement of the behavior delivery and release targeting protein [107].

3.3.2 Wound Dressings

During wound healing, inflammation, debridement, proliferation of granulation tissue, and reepithelialization are the normal processes that occur [108]. A desirable gel for wound dressing should guarantee the suitable moisture and constant temperature of the wound, allow exchange of gases between the wound and outside, adsorb excess exudates, prevent the bacteria from infracting and contamination from the wound, accelerate healing, and relieve pain [109, 110]. It should also be nontoxic, non-adherent, and easily removed without trauma. Diverse species of hydrogel based on synthetic or natural polymers or a combination for dressings have been investigated so far and are commercially purchased.

However, cellulose itself has no antimicrobial activity; some antimicrobial agents can be incorporated into the cellulose hydrogels to protect the wound

against bacteria [111]. Maneerung et al. impregnated silver nanoparticles into BC gels; the freeze-dried silver nanoparticle and BC hybrid exhibited the superior antimicrobial activity against *Escherichia coli* (Gram-negative) and *Staphylococcus aureus* (Gram-positive) [111]. Similarly, Li et al. synthesized cellulose–silver gels with microwave-assisted synthesis, possessing a high thermal stability and antimicrobial property [112]. ZnO/BC gels were synthesized by ultrasonic-assisted route and the composited hydrogel as well as showed excellent antibacterial activity against *Escherichia coil* and *Staphylococcus aureus* with high efficiency [69]. Moreover, the mechanisms of the antibacterial abilities of ZnO and Ag nanoparticles were distinguished: for the ZnO, it is considered that decorated ZnO nanoparticles can react with water molecules, resulting in the production of reactive oxy-radicals or hydroxyl radicals which could induce oxidative injury inside bacterial cells. For the Ag NPs, it was able to directly penetrate inside the bacteria or paste to the surface of the bacteria destroying permeability and respiration functions. Eukaryotes can undertake higher concentrations of ZnO or Ag NPs than bacterial cells to achieve appropriate toxic effects, leading to biocompatibility of the materials for human cells. Chiaoprakobkij et al. developed the novel BC/alginate sponges without the antibacterial property; such gel can be applied as a temporary wound dressing material due to its many advantages including appropriate cell attachment, skin tissue compatibility, excellent water uptake ability, high mechanical strength, and good tear resistance properties [113]. Chitosan is antimicrobial, permeable, nonirritating, and without allergic reactions, especially the desired ones for wound dressings [114]. Hybridization with cellulose can improve the healing effect due to the high bioactivity of cellulose whose main components are collagen and a few protein amylases. The behavior of wound dressings consistent with the tissue scaffolds is connected with the drying technology and water retention. Dressings with nanopores or porogen-induced pores obtained from air-drying are twice stronger than the porous ones obtained by freeze-drying. Mohamad et al. synthesized BC/acrylic acid hydrogel by electron beam irradiation; the as-prepared hydrogel exhibited suitable physical and mechanical characteristics and was able to accelerated burn wound healing (Fig. 6h–k) [115].

3.3.3 Tissue Engineering

Recent tissue engineering has been a fascinating application since hydrogels catch the attention of researchers, where they are used as skeletons to imitate the roles of extracellular matrices and to engineer new tissues; these skeletons support space and nutrients for new formation of tissue and potentially control the structure and function of the engineered tissue in situ or in vitro [1, 8]. Now, hydrogel skeletons are at near clinical uses to engineer many tissues in the body including the cartilage, bone, muscle, skin, fat, artery, liver, ligament, tendon, bladder, and neurons [116, 117].

Cellulose-based hydrogel skeletons should appropriately satisfy a great deal of design criteria of multifunction and promotion of new tissue formation, including processability, biodegradability in tissue engineering system, and cell adhesion

ability [118]. Saska et al. prepared BC gels by cross-linking of type I collagen; the BC-collagen hydrogels were cultured on high protein content and ALP activity at day 17 in cells, suggesting this gels enabled the growth of the osteoblastic phenotype in vitro [119]. It was shown that the optimal pore sizes of skeletons in tissue engineering were to be 5 μm for neovascularization, 20–125 μm for regeneration of the skin, and 100–350 μm for regeneration of the bone [120–122]. It was suggested that the microarchitecture played a role in tissue regeneration; the bone can be regenerated in freeze-dried skeletons with medium pore sizes as low as 16 μm via hematoma osteoinduction instead of osteoconduction in big pores [123]. Pore sizes of hydrogels were impacted by various factors such as drying methods, biopolymer concentration, and cross-linking degree, and they can also be improved by adding a "porogen." Svensson et al. prepared native BC hydrogels, which supported chondrocyte proliferation at levels of approximately 50% of the native tissue substrate, collagen type II, and it showed significantly higher levels of chondrocyte growth contrasted to tissue culture plastic and alginate (Fig. 6i–l) [124].

3.4 Other Applications

Cellulose-based hydrogels are applied widely in many other diverse applications. One of the most potential applications is energy storage systems such as capacitor or battery. Yamazaki prepared acidic cellulose–chitin hybrid gel electrolyte for a double layer with a high ionic conductivity at room temperature, and the capacitor using the acidic cellulose–chitin showed the higher special capacitance and a better cycle performance than with the H_2SO_4 [125]. These indicated that the acidic cellulose–chitin gel electrolyte has the practical applicability with excellent stability and working performance in capacitors. Lee et al. investigated the swelling behavior of carboxymethyl cellulose that influences a natural graphite suspension from the aspects of stability and chemical properties for Li-ion battery; experiment results displayed that Li/organic electrolyte/nature graphite with the swelling cellulose has exhibited an initial discharge capacity above 340 mAh g^{-1} and an improved charge–discharge efficiency [126]. Combining with inorganic catalysts, cellulose-based heterogeneous catalysis has attracted some interests of researchers recently. Kemell et al. prepared the TiO_2/cellulose composite and verified its photocatalytic activity of photocatalytic reduction of Ag(I) from to Ag nanoparticles on the TiO_2 surface [127]. The TiO_2/cellulose composites were more mechanically stable than the free-standing TiO_2 replicas and potentially suitable as lightweight, high-surface-area photocatalysts.

Nanometal and metal oxides, carbon materials, conducting polymers, and ionic liquids can be mixed (through doping, blending, or coating) into the cellulose frameworks. Such composites form a biocompatible surface for microelectronic devices, implantable biosensors, and neuronal prostheses. Van den Berg et al. prepared cellulose nanofibers and conducted π-conjugated polymer nanocomposites, which exhibited the electronic property of the conducted polymers as well as the outstanding mechanical property of the cellulose networks

[128]. Besides, cellulose could serve as template to synthesize diverse nanocrystals that present nanoscale size- and shape-dependent properties. Olsson et al. constructed flexible magnetic aerogels by cellulose nanofibrils as a facile template approach; due to the BC, they have a crystal structure with high-molar-mass, hydrogen-bonded chains in an extended chain conformation [129]. Lin et al. developed a general strategy to craft a series of plain nanorods, core–shell nanorods, and nanotubes with accurately controlled dimensions and compositions with well-defined structures and narrow molecular weight through amphiphilic cellulose-g-(PAA-b-PS) as nanoreactors [130].

Cellulose hydrogels having strong fluorescence have been successfully fabricated by Chang et al. Photoluminescence (PL) spectra indicated that the cellulose matrix in the composites performs a significant role in the protection of the CdSe/ZnS structure [63]. The cellulose–QD hydrogels exhibited strong PL emission and nearly pure color from green to red, depending on the size of the QDs. Moreover, the hybrid hydrogels possessed a good transparence and compressive strength. Phase change materials, widely applied in energy fields as potential heat energy storage and release media with effective thermal management, have attracted more and more attention. Yang et al. combined defect-free graphene with microcrystalline cellulose for phase change composites; the lightweight cellulose/graphene gel exhibited a high thermal conductivity of 1.35 W m^{-1} K^{-1} [131].

4 Conclusions

We have discussed on solvents which have been used for the dissolution of native cellulose or cellulose derivatives, and there are only a few solvents including polar solvents (such as *N*-methylmorpholine oxide, dimethylacetamide), ionic liquids (such as 1-butyl-3-methylimidazolium chloride or 1-allyl-3-methylimidazolium chloride), and alkali/urea to date. Blending two or more polymers (such as chitosan or/and polyvinyl alcohol) endows cellulose hydrogels with high adsorption ability for anionic and cationic dyes, and magnetic inorganic nanoparticles like Fe_3O_4 grafting polymer networks make hydrogels to be easily recycled after adsorption. The abundant functional groups and specific surface area of cellulose-based hydrogels guaranteed their removal efficiency for heavy metal ions. Hydrogels can also store large amounts of water even under compression; meanwhile they swell after adsorbing water from xerogel (with a fine dimensions), so they can serve as water superabsorbents for personal care and hygiene, agriculture, and biomedical applications (changing the structure and morphology of the network, subsequently controlling their diffusion properties, pH-triggered, targeted drug delivery, guaranteeing the suitable moisture and constant temperature of the wound, allowing exchange of gases between the wound and outside, absorbing excess exudates, preventing the bacteria from infracting and contamination of wound dressings, and are used in tissue engineering). Moreover, cellulose hydrogels are able to be energy storage systems, grafted with inorganic catalyst (TiO_2, Ag nanoparticles) for catalysis, grafted with quantum dot (CdSe/ZnS) for fluorescent light, and so on.

5 Perspective

For future studies, more attentions should be focused on green chemistry such as using safe solvents, nontoxic cross-linkers, and green synthesis and low-energy processing. It is necessary to prepare modified hydrogels with unique characteristics such as highly elastic, super-stretchable, and self-healing properties and to develop novel biopolymer isolation methods to produce cellulose with high molecular weights and such unique hydrogels. For water purification, cellulose-based hydrogel should improve their efficacy, selectivity, and recycling for the sake of economical development. For biomedical fields, parameter-based (such as pH) trigger release should accurately arrive at targeted sites, and injected hydrogels without the requirement of surgery form safely inside the body applied for drug release or tissue engineering. Moreover, degradation of hydrogel in vivo could be considered with a controlled manner in both applications. New applications of cellulose-based hydrogels (such as solid-state hydrogels for energy systems, flexible electronic device) could be further investigated. Undoubtedly cellulose-based production will be available to substitute for petroleum-based materials in near future.

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Structure-Property Relationships in Cellulose-Based Hydrogels

3

Diana Elena Ciolacu

Contents

Abstract

Hydrogels are widely used for different biomedical applications, due to their ability to absorb, retain, and release water solutions in a reversible manner and in response to specific environmental stimuli. The review is focused on the preparation methods, main characteristics, as well as biomedical applications of hydrogels prepared from the most abundant biopolymers on earth, cellulose. The chapter emphasizes the latest developments in the design and manufacture of cellulose-based hydrogels. The preparation of hydrogels without covalent cross-links (physical hydrogels) and with covalent cross-links (chemical hydrogels) is discussed. The behavior of gels upon coagulation and the swelling

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capacity in water were analyzed. A systematic investigation into the structure and physical-chemical properties of cellulose-based hydrogels was performed in order to describe the relationships between the network structure and gel properties. The degree of cross-linking of the hydrogels, the morphology of the three-dimensional (3D) matrices, the bulk geometry, and the description by different complementary techniques which offered insight into structure-property relationships of hydrogels are reviewed. The sorption properties of cellulose-based hydrogels and the effect of the design parameters of hydrogels on their biomedical applications are also discussed.

Keywords
Cellulose · Hydrogel · Gelation · Cross-linking · Swelling · Drying · Morphology

1 Introduction

Hydrogels are defined as a hydrophilic polymers structure, capable to absorb and retain a relatively large amount of water or aqueous fluids (up to 10 g/g for ordinary absorbent hydrogels or more for superabsorbent hydrogels). The water-absorbing capacity and mechanical property of hydrogels usually rely on their three-dimensional (3D) network structure which can be driven by both chemical and physical interactions [1–3].

The classification of hydrogels depends on their physical properties, nature of swelling, method of preparation, origin, ionic charges, sources, rate of biodegradation, and the nature of cross-linking [4]. A detailed classification of hydrogels is presented in Fig. 1.

On the basis of the preparation method, the hydrogels can be divided into (i) *physical hydrogels*, which are achieved via physical processes, such as hydrophobic association, chain aggregation, crystallization, polymer chain complexion, and hydrogen bonding, and (ii) *chemical hydrogels*, formed by chemical covalent cross-linking. Physical hydrogels are reversible due to the conformational changes, while chemical hydrogels are permanent and irreversible because of configurationally changes [4]. Concerning the source, hydrogels can be divided into those obtained from natural polymers, synthetic polymers, and the hybrid hydrogels. Over the past two decades, natural polymers have been slowly replaced by synthetic ones or were hybridized to provide a higher service life, gel strength, and water absorption capacity [5].

The physicochemical properties of hydrogels are based on a number of factors, including the chemical nature of the monomer, the method of polymer synthesis, their molecular weight due to the reaction environment, and macromolecular structure. On the other hand, the physical structure of the polymer relies on the strength of the covalent bonds, the rigidity, and intermolecular force strength within the polymer chain [6].

The volume or mass-swelling ratio of the hydrogel is the most important variable to be evaluated for given environmental conditions, as it affects the diffusive,

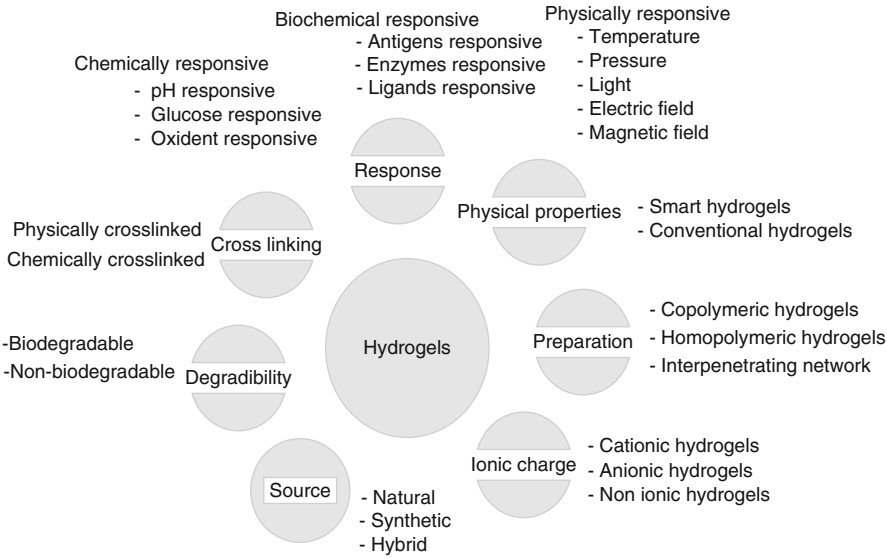

Fig. 1 Classification of hydrogels based on the different properties. (Reprinted with permission from [4]. Copyright © 2015, Elsevier.)

mechanical, optical, acoustic, and surface properties of the hydrogel itself. The amount of water retained by the mesh of the hydrogel network depends on the structure of the polymer network itself and on the environmental conditions, such as the temperature, pH, and ionic strength of the water solution in contact with the polymer [7].

The interactions responsible for the water sorption include capillary, osmotic, and hydration forces, which are counterbalanced by the forces exerted by the cross-linked polymer chains in resisting expansion. The equilibrium swollen state depends on the magnitudes of these opposing effects and determines to a large extent some important properties of the hydrogel, including internal transport and diffusion characteristics and mechanical strength. Many of these properties are governed not only by the degree of swelling, but also directly by the chemical nature of the polymer network and the network morphology [8].

The physical or chemical processes are adjustable based on the desired characteristics, such as structure, matrix density mechanical strength, biocompatibility, and biodegradability, which are subjective to the specific field and function to which they will be applied [9].

Since environmentally friendly products and processes are of great importance nowadays, much industrial research has focused attention on the synthesis of novel cellulose-based hydrogels. In fact, cellulose is a natural polymer that can be employed as renewable-based polymeric material with biodegradable properties [7].

The hydrogels from natural polymers, especially those from cellulose, are promising for their application in biomaterial field, because of their unique advantages,

such as abundance, non-toxicity, biocompatibility, biodegradability, and biological functions [10–12].

Innovative cellulose-based hydrogels have been developed either as water absorbents for specific applications, including personal hygiene products, underwater devices, body water retainers [7, 13], or biomedical devices, as ocular bandages [14], artificial cartilage [15, 16], controlled drug delivery [17–19], scaffolds for regenerative medicine [20, 21], stomach bulking agents [22], and wound dressings [12, 23, 24].

This chapter explores the synthesis and design of cellulose-based hydrogels, including pure cellulose and cellulose composite. The recent developments with emphasis on the fabrication, properties, and possible applications are highlighted. In particular, the attention is focused on the structure-property relationships of hydrogels and their biomedical and pharmaceutical applications.

2 Cellulose and Its Applications

Cellulose is the most common organic polymer and is considered an almost inexhaustible source of raw material for the increasing demand of environmentally friendly and biocompatible products [25]. This biopolymer exhibits some excellent properties, such as mechanical robustness, biodegradability, hydrophilicity and biocompatibility, properties responsible for the extensive use of cellulose in a wide spectrum of applications that include pharmacy, agriculture, medical science, industries, and many other related branches [26].

In contrast with its vast potential of applications, it is known that there are certain difficulties in producing cellulose-based products such as films, fibers, membranes, hydrogels, and beads, due to its partially crystalline structure and strong hydrogen bonds. The long-chain cellulose polymers consist of D-glucose subunits which are linked together by β-1,4 glycosidic bonds. These linear polymers are linked together by different inter- and intramolecular bonds, which allow them to be packed side by side in planar sheet and bundled into microfibrils (Fig. 2). Hence, the cellulose is insoluble in water as the hydroxyl groups in sugar chains are bonded to each other, making a hydrophobic scenario [27].

Unlike other types of water-soluble polysaccharides, cellulose requires separate solvent systems for its dissolution, which have remained limited because of the lack of a suitable solvent. In the early days, the use of concentrated sodium hydroxide (NaOH) solution as cellulose solvent interested researchers due to numerous applications of cellulose treatments with NaOH solution in fiber modification, dissolution, and regeneration [28]. Moreover, there were other solvent systems, from which the most widely used until the 1950s was cuprammonium hydroxide (Cuam) solution, while the aqueous solutions of cupriethylenediamine (Cuem) complex and some tetraalkylammonium hydroxides were used as solvents for analytical purposes in those days. In the decade of the 1960s, the discovery of numerous metal-complex solvents brought in more variations of cellulose solvents from which the most important were ferric sodium tartrate (FeTNa) and cadoxen solvent systems.

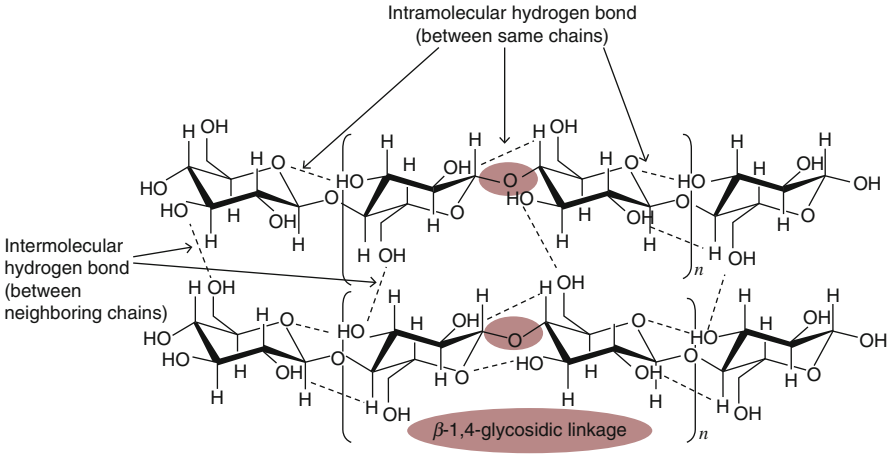

Fig. 2 Chemical structures of cellulose chains. (Reprinted with permission from [27]. Copyright © 2014, Hindawi.)

In recent years, considerable attention has been directed to several cellulose-solvent systems for dissolving cellulose, such as N,N-dimethylacetamide/lithium chloride (DMAc/LiCl) systems [29, 30], *N*-methylmorpholine-*N*-oxide (NMMO) [31, 32], tetrabutylammonium fluoride/dimethylsulfoxide (TBAF/DMSO) [33], paraformaldehyde/dimethylsulfoxide (PF/DMSO), triethylammonium chloride/dimethylsulfoxide (TEAC/DMSO) [34], ionic liquids [35–37], and alkali aqueous solutions [38–41].

In spite of its poor solubility characteristics, cellulose has versatile uses in many industries such as veterinary foods, wood and paper, fibers and clothes, cosmetic, and pharmaceutical industries [42, 43].

Generally, cellulosics are strong, low cost, reproducible, recyclable, and biocompatible [44]. Thanks to all of these properties, they are often used in various biomedical applications such as blood purification membranes in artificial kidneys [45], membranes in plasmapheresis [46], body water retainers [13], ocular bandages [14], artificial cartilage [15], scaffolds for regenerative medicine [47], and stomach bulking agents [48].

3 Synthesis of Cellulose II-Based Hydrogels

Cellulose hydrogels are a special class of cellulose materials which can be based on:

- **Cellulose I**, case of bacterial cellulose (BC) or cellulose nano-/microfibrils (CNF) or cellulose nanocrystals (CNC) [49, 50]
- **Cellulose II**, prepared via cellulose dissolution-coagulation route [51, 52]

Both types show high water retention, from several hundred to several thousand percent.

Cellulose-based hydrogels can be obtained via either physical or chemical stabilization of aqueous solutions of cellulosics. Additional natural and/or synthetic polymers might be combined with cellulose to obtain composite hydrogels with specific properties [7]. The synthesis of cellulose-based hydrogels generally consists of two steps [53]: (i) dissolution of cellulose fibers or powder, and (ii) chemical and/or physical cross-linking, in order to obtain a three-dimensional network of hydrophilic polymer chains, which is able to absorb and retain a significant amount of water. By tuning the cross-linker and cellulose concentrations, it is possible to optimize the hydrogel mechanical properties and swelling capabilities.

3.1 Dissolution of Native Cellulose

Due to its highly extended hydrogen-bonded structure, cellulose is very difficult to dissolve in common solvents, and thus only few solvents have been used for it solubilization.

A series of solvent systems such as LiCl/DMAc for cellulose powder, paraformaldehyde (PF)/dimethyl sulfoxide (DMSO), and triethylammonium chloride (TEAC)/DMSO for cellulose pulp have been used to fabricate cellulose hydrogels [52]. The obtained physical properties of hydrogels, such as transparency, strength, and water content, mainly depend on the composition of the coagulation/regeneration bath, while in the case of a nonaqueous solution, the maximum transparency of the hydrogels was obtained. A novel method, deionization of the cellulose/LiCl/DMAc solution with ion exchange resins, has been reported for preparation of gel beads that appear colorless and transparent without a fibrous texture compared with the "water-coagulated gel," probably because the molecular association (crystallite formation) precedes the phase separation during ion exchange [54].

By using N-methylmorpholine-N-oxide (NMMO), with low toxicity, high thermal stability, and the possibility of being recovered and reused, an opalescent cellulose-based hydrogel was obtained by adding excess water into the cellulose/NMMO/water solution [55].

Another solvent system for cellulose dissolution and gelation is ionic liquids (ILs). The preparation of the clear and homogeneous cellulose solution was done under mild conditions by using N-ethyl-N′-methylimidazolium methylphosphonate ($[C_2mim][(MeO)(H)PO_2]$) [56]. The mechanical strength of cellulose hydrogels strongly depends on the concentration and degree of polymerization (DP) of cellulose. Moreover, the mechanical property of cellulose gel remained unaltered after treatment with boiled water, indicating the excellent thermal stability of cellulose hydrogels. Various ILs used for cellulose dissolution have been applied in the preparation of cellulose-based hydrogels, such as 1-ethyl-3-methylimidazolium acetate ($[C_2mim][OAc]$) [57, 58], 1-butyl-3-methylimidazolium chloride ($[C_4mim]Cl$), and 1-allyl-3-methylimidazolium chloride ([Amim]Cl) [54].

A recent alternative for cellulose solubilization and hydrogel preparation is the alkali aqueous system, which uses freezing at low temperature followed by the thawing of the mixture, instead of stirring at room temperature or high temperatures. The obtained physically cross-linked hydrogels have a dense texture with heterogeneous morphology, which presents pores between 4 and 8 μm [59]. The bulk density for the physical cross-linked hydrogel is twice higher than for chemical cross-linked hydrogel. An interesting fact is that the physical cross-linked hydrogels are opaque, while chemical cross-linked hydrogels become more and more transparent, by increasing the cross-linker concentration (epichlorohydrin).

The cellulose dissolution at low temperature arises as a fast dynamic self-assembly process among solvent small molecules (NaOH, urea, and water) and the cellulose macromolecules [38]. Cellulose in solution behaves as random coils, semiflexible chains, or entangled chains, and the degree of entanglement depends on the polymer concentration. The gel structure becomes more and more organized and stable as cellulose concentration increases due to the higher degree of entanglements and the more hydrogen-bonding interactions that exist. Cellulose hydrogels can be formed via destructing the stability of cellulose solution by increasing the temperature to 50 °C or reducing it to −20 °C [52]. When a low temperature was used, active NaOH hydrates were bound to cellulose to bring it into the solvent, whereas urea hydrates served as the hydrogen-bonding donor and receptor to prevent the approach toward each other of the cellulose molecules, leading to a good dispersion of cellulose in the solution. At elevated temperature the NaOH and urea hydrates bounded on the cellulose chains were perturbed, so the junction between cellulose molecules occurred as a result of the self-association force of cellulose, resulting in the formation of a network structure [60].

3.2 Physical and Chemical Gelation

A key step in the formation of any hydrogel is "gelation," which can be interpreted as the interconnecting of the macromolecular chains in some manner, such that essentially the whole structure becomes linked together [61, 62].

Cellulose in solution behaves as random coils, semiflexible (or semirigid) chains, or entangled chains, and the degree of entanglement depends on the polymer. While polymer solutions of low concentrations are completely isotropic, with increasing polymer concentration, the transition from solution to a liquid crystalline gel takes place followed by gelation into a solid gel that has an anisotropic structure [54]. The gel structure becomes more and more organized and stable as biopolymer concentration increases due to the higher degree of entanglements and the more hydrogen-bonding interactions that exist [58].

The gelation mechanism involves hydrophobic associations among the macromolecules possessing the methoxy group. At low temperatures, polymer chains in solution are hydrated and simply entangled with one another. As temperature increases, macromolecules gradually lose their water of hydration, until polymer-polymer hydrophobic associations take place, thus forming the hydrogel network [51].

The stability of the hydrogel can be enhanced by coagulation in different anti-solvents, as water [57], ethanol [63], methanol [64], H_2SO_4/Na_2SO_4 [65], or by curing (i.e., keeping the solution at various temperatures between 5 °C and 60 °C) [66].

Covalent cross-linking has emerged as the preferred means of converting suitable hydrophilic polymers into absorbent hydrogels, and the cross-linking optimization implies a balance between achieving high absorbency, suitable mechanical strength, and minimizing the amount of material that dissolves into the bulk of the liquid when a highly absorbent hydrogel is in use [61, 67, 68]. Stable and stiff networks with irreversible cross-linking bonds between the cellulosic chains can be obtained by chemical cross-linking reaction in the presence of chemical agents (epichlorohydrin, aldehydes and aldehyde-based reagents, urea derivatives, carbodiimides, and multi-functional carboxylic acids) or physical treatments (i.e., high-energy radiation) [51].

Intense research has focused on the preparation of cellulose-based hydrogels via cellulose dissolution/coagulation route, with continuous improvements of efficiency in solvents such as NaOH aqueous solutions and similar systems (i.e., NaOH/urea, NaOH/urea/thiourea, LiOH/urea) [69–72], which are non-derivatizing, inexpensive, and nontoxic cellulose solvents. In the presence of 7–9 wt% NaOH-water solvent, cellulose solutions undergo a physical gelation with the increase of time and temperature [73].

Gelation occurs due to cellulose chains self-association because of the preferential cellulose-cellulose and not cellulose-solvent interactions; this physical gelation is accompanied by a micro-phase separation [59]. By adding epichlorohydrin (ECH) as cross-linker in cellulose-NaOH-water solution, cellulose chains become chemically cross-linked. Two mechanisms are therefore present and can possibly compete: physical gelation due to chains self-association and chemical cross-linking (Fig. 3a).

It was suggested that chemical bonds act as "spacers" preventing, at least partly, the self-association of cellulose chains, as shown on a sketch in Fig. 3a. A schematic presentation of the structure of physical and chemical cellulose gels is shown in Fig. 3b. Chemical gelation (i) perturbs cellulose chains self-association and packing which leads to the decrease of crystallinity, (ii) leads to a more homogeneous morphology which results in transparent swollen coagulated cellulose hydrogels, and (iii) increases swelling in water and adsorption of water vapors due to a more porous structure. As a consequence, the difference in the structure and swelling of physical vs. chemically cross-linked cellulose influences their release properties: in chemically cross-linked cellulose, a larger amount of drug can be loaded, and the release kinetics is faster compared to physically cross-linked matrix. By varying cellulose concentration and the amount of cross-linker, it is possible to prepare versatile cellulose hydrogels and dry porous networks with controlled morphology and porosity.

Compared to chemically cross-linked hydrogels which require covalent bonding for the formation of 3D networks, physically cellulose-based hydrogels are formed mostly by hydrogen bonding via a self-assembly process.

In the presence of strong organic solvents such as N,N-dimethylacetamide (DMAc)/LiCl, the gradual dissolution of cellulose starts by the formation of hydrogen bonding between the hydroxyl protons of the anhydroglucose unit within cellulose with the Cl^- in LiCl. The Cl^- is then attracted to the $(LiDMAc)^+$

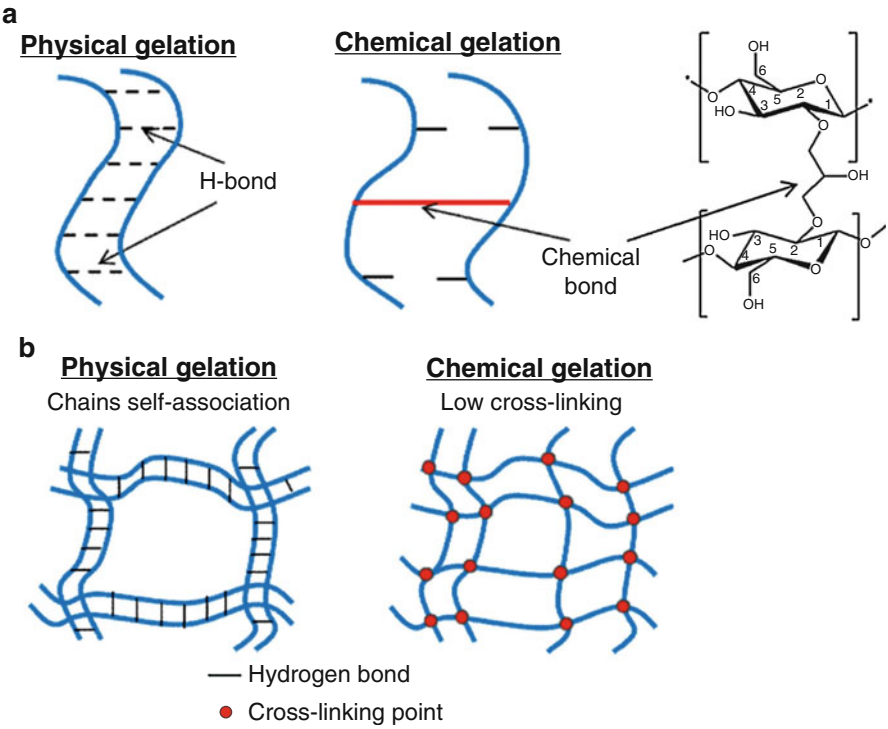

Fig. 3 (**a**) A sketch of network formation in cellulose solutions: physical gelation via self-association of chains and chemical cross-linking, (**b**) a schematic presentation of the structures of physical and chemical cellulose gels. (Reprinted with permission from [59]. Copyright © 2016, Elsevier.)

macrocation with the formation of repulsive forces between different segments of the host cellulose. The repulsive forces will then open more micropores, allowing more solvent to penetrate into the cellulose matrix. Due to the anhydrous nature of the above solution, the presence of moisture leads to the regeneration of hydrogen bonding between the dissolved cellulose segments, that is, gelation [62]. Throughout this process, the cellulose main chains assemble into a 3D network structure by reforming hydrogen bonds between various OH^- groups on the anhydroglucose units. Due to the fast reaction kinetics and high hydrophilicity of the anhydroglucose units, large amounts of moisture are trapped in the gel. Since the water molecules are present mostly between the anhydroglucose chains, the drying of hydrogels will lead to the formation of new hydrogen bonds and cause the collapse of micropores.

Ionic liquids enable the dissolution of cellulose by disrupting and breaking hydrogen-bonding networks. By using N-ethyl-N′-methylimidazolium methylphosphonate ($[C_2mim][(MeO)(H)PO_2]$), a 10 wt% homogeneous cellulose solution, under mild conditions, has been prepared [56, 74].

Recently, cellulose-based hydrogels was prepared through the physical aggregation of polymer chains determined by hydrogen bonds, crystallization, helix

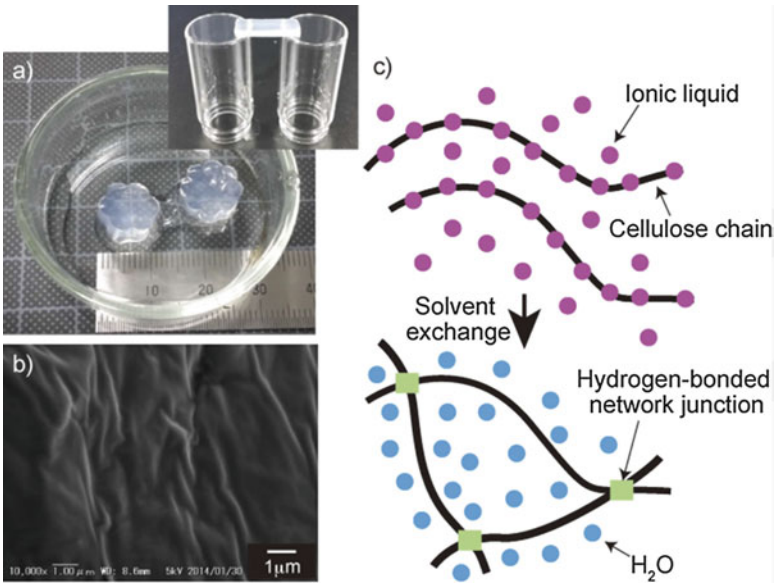

Fig. 4 (**a**) Optical images of flower-shaped cellulose hydrogels prepared from 5 wt% IL solution of WP. The inset is an optical image of bridged cellulose hydrogel. (**b**) SEM image of the surface of dried cellulose hydrogel. (**c**) Schematic gelation process of the cellulose solution. (Reprinted with permission from [37]. Copyright © 2016, John Wiley & Sons, Inc.)

formation, and complexation (Fig. 4). Cellulose was completely dissolved in $[C_2mim][(MeO)(H)PO_2]$ through the breaking of the hydrogen bonds among cellulose backbones, and the dissociated cellulose chains were partially aggregated during the solvent exchange process by treating them with methanol vapor. The structure was set uniformly by a spinodal decomposition-type phase separation during the treatment with methanol vapor, and the partial aggregation of cellulose chains acted as a network junction point in three-dimensional networks [37].

Cellulose hydrogels containing 95–99% water have been fabricated using the solvent exchange of homogeneous cellulose solutions without the use of chemical cross-linking (Fig. 4c). Water was incorporated within the three-dimensional network of the hydrophilic cellulose chains containing hydrogen-bonded network junction points.

4 Synthesis of Cellulose I-Based Hydrogels

4.1 Nanocellulose Hydrogels

Nanocelluloses are a class of natural materials derived from cellulose, the most abundant renewable polymer on earth, which include cellulose nanofibrils (CNFs) and cellulose nanocrystals (CNCs). Cellulose nano- and microfibrils are

substructural elements of cellulosic fibers that can be mechanically disintegrated (high-pressure homogenization and refining, microfluidization, grinding, cryocrushing, and high-intensity ultrasonication combined with chemical or enzymatic treatments) from the cell wall matrix, while cellulose nanocrystals are isolated from microcrystalline cellulose using acid hydrolysis and/or sonication process.

The most crystalline form of cellulose is cellulose nanocrystals (CNCs), which are shorter than the nanofibrils. In addition, CNCs present many advantages, such as nanoscale dimension, high specific strength and modulus, high surface area, unique optical properties, and therefore wide possibilities of application [75]. Cellulose sources are variable and their degree of crystallinity strongly influences the dimensions of the liberated crystals [49, 76].

The physical and chemical properties of nanocelluloses have enabled their use in a wide variety of hydrophilic and hydrophobic composite matrices and hybrid materials, including hydrogels and aerogels. Furthermore, their high surface area-to-volume ratio enables enhanced interactions with, and binding to, polymers, other nanoparticles, and small molecules [77].

Hydrogels prepared only from CNCs at a concentration above 10 wt% will enter an aggregated gel-like phase [78, 79]. Other methods to prepare CNC hydrogels are by destabilizing the CNC suspensions with salt or acid, or by cross-linking of CNCs with multivalent ions or chemical bonds [80, 81]. In practice, the CNC concentration at which a gel is formed may be manipulated via changing the solution conditions, surface modifications, and/or adding adsorbing or non-adsorbing water-soluble polymers [82, 83]. It was observed that by increasing the ionic strength of CNC suspensions via salt addition, the electrostatic repulsion was suppressed, which led to dominant attractive forces (e.g., van der Waals and hydrogen bonding) and, consequently, to gelation. Thus, the increasing of the charge number and the radii of the ions both led to increases in gel stiffness [79, 81].

Due to their increased flexibility and tendency for entanglement, cellulose nanofibrils are more liable to hydrogel formation than CNCs.

The NFC suspensions (Fig. 5) bear the appearance of highly viscous shear-thinning transparent gels and have high aspect ratios and specific surface areas combined with remarkable strength and flexibility, low thermal expansion, high optical transparency, and specific barrier properties [84].

Typical CNF hydrogels contain 0.05–6 wt% CNFs, but CNF gels have been reported at concentrations of 0.125 wt%, following an enzymatic treatment and homogenization of bleached sulfite pulp [85]. These hydrogels are of two orders of magnitude concentration lower than that required for CNC gelation.

Hydrogels with oriented fibrils can be prepared by flow focusing CNF suspensions, followed by inducing gelation through pH reduction or salt addition, and these can be used as templates for anisotropic nanocomposites (Fig. 6) [79, 86, 87].

The flow-induced CNF-oriented alignment displayed exceptional mechanical properties that were enhanced as the degree of orientation was increased; however, filament stability drastically decreased in the presence of water, representing a key limitation of this technique [88]. Similar to most CNC hydrogels, CNF hydrogels lack macroscopic structure or hierarchy, which is a

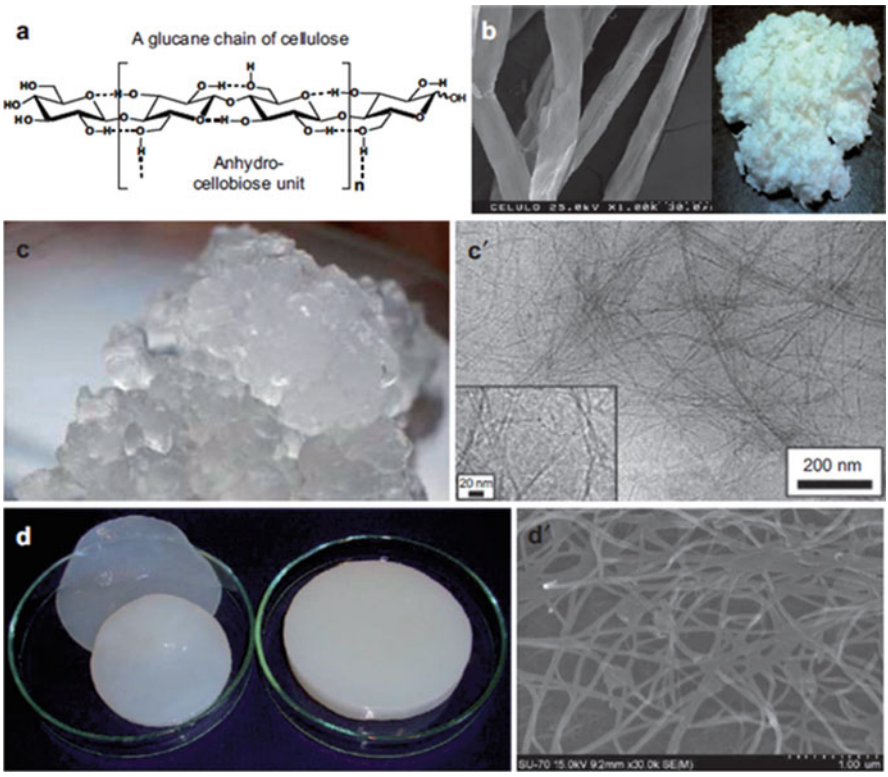

Fig. 5 Images of cellulose. (**a**) A glucan chain of cellulose with repeating anhydrocellobiose units. (**b**) Macroscopic and SEM images of conventional pulp fibers. (**c** and **c′**) Macroscopic and SEM images of NFC. (**d**) Image of BC. (**d′**) SEM image of BC. (Reprinted with permission from [84]. Copyright © 2011–2017, Walter de Gruyter GmbH.)

serious disadvantage when developing biomimetic materials or hydrogels for many biomedical applications [79].

4.2 Bacterial Cellulose Hydrogels

Bacterial cellulose (BC), also known as microbial cellulose, is produced by different bacteria genera, such as *Gluconacetobacter*, *Sarcina*, and *Agrobacterium*, but *Gluconacetobacter xylinus* is probably the most commonly referred strain in this context [84]. A consideration of the nanocrystallinity of cellulose leads directly to BC, because this is synthesized in highly crystalline forms and in very high yields by *Gluconacetobacter xylinus* (*G. xylinus*), which is the most widely studied source of BC [89, 90]. BC can be produced as a highly swollen hydrogel and, depending on the static or agitated nature of the culture media, as a membrane (Fig. 5d, d′) or in the

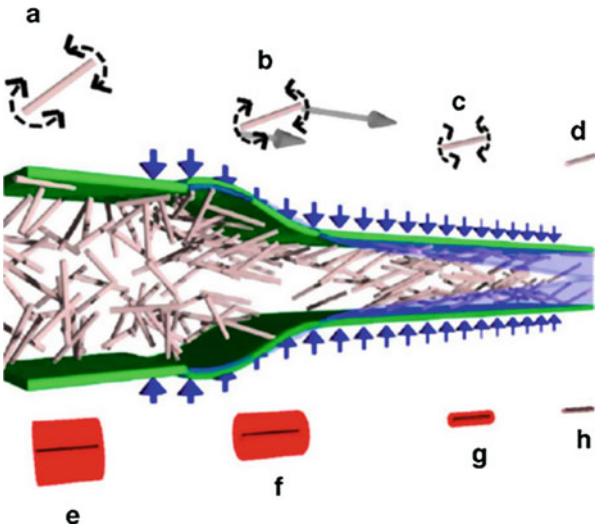

Fig. 6 Illustration of the flow focusing CNF hydrogel assembly process. The diffusion of Na+ ions into the flow channel is depicted by blue arrows, the concentration of which increases as the channel narrows, shown by the shaded blue area. (**a**) Initially, CNFs undergo Brownian diffusion, which decreases as (**b**) individual particles undergo hydrodynamically induced alignment. (**c**) Particles are constrained uniaxially and (**d**) "frozen" in place as the increased Na+ ions cause gelation of the system. (**e**–**h**) The electrostatic repulsion and the Debye length of CNF fibrils (shown in red) decrease along the channel as surface carboxyl groups become uncharged/shielded. (Reprinted with permission from [79]. Copyright © 2017, American Chemical Society.)

form of small beads. More precisely, BC is a 3D network consisting of nano- and microfibrils with the dimensions of 3–4 nm thickness and 70–80 nm length (Fig. 5d′); that is, the fibrils are approximately 1000 times thinner than typical plant cellulose fibrils. These dimensions explain the unique properties of BC. Additionally, BC is free of lignin, hemicelluloses, and other natural components usually associated with cellulose isolated from the cell wall of plants [84]. BC has been shown to have superior properties compared to plant-derived cellulose, such as high surface area, degree of polymerization, wet tensile strength, purity, crystallinity, and nanostructured fibers [91]. BC is known to be biocompatible, perhaps because of its flexibility and porosity, resembling properties of collagen in the human body [92].

A detailed analysis of the water interaction properties in as-biosynthesized BC gels indicates that only about 10% of the 99 wt% water present in BC gels behaved like free bulk water, and the majority of the water molecules in the gels are more or less tightly bound to the cellulose [93]. In a recent study, BC nanocellulose was shown to effectively control the uptake and release of albumin and demonstrated the retention of protein integrity, which can sometimes be compromised during the manufacturing process [94].

On the basis of the high purity and unusual physicochemical properties, BC-based hydrogels offer a wide range of applications in biomaterials fields such as tissue engineering scaffold [95], meniscus implant [96], and dental implants [97].

5 Multipolymer Hydrogels Based on Cellulose

The multipolymer hydrogels have been prepared from cellulose and other polymers by interpenetrating polymer networks (IPNs) technology, in order to combine the different properties of cellulose and other polymers. Generally, the preparation processes include the dispersion or dissolution of two or more polymers (usually using the same solvent) and the cross-linking step.

Cellulose can be blended with *natural biodegradable polymers*, such as chitin [98], chitosan [99], starch [100], xanthan [101], lignin [102], and alginates [103].

The blending of cellulose and chitin in the same solvent system is an effective way to produce phase-separated composite hydrogels. Chitin/cellulose beads have been prepared by coagulating a mixture of 4 wt% cellulose solution and 2 wt% chitin solution in 6 wt% NaOH/5 wt% thiourea aqueous system [52]. The adsorption ability of obtained beads is higher than that of pure chitin flakes, owing to the relatively large surface area and their high hydrophilicity. The hydrophilic skeleton and microporous-network structure of cellulose improve the adsorption ability of chitin [104].

Cellulose/chitosan hydrogel beads have been prepared by blending cellulose powder with chitosan solution, in the presence of ethylene glycol diglycidyl ether, as cross-linker. These hydrogel beads are denser, have improved chemical stability in the solutions with pH values down to 1, and have high adsorption capacity for Cu adsorption [99]. Cellulose/chitosan hydrogels have been also prepared when the polymers were mixed in NMMO and then processed under a pressure of 70 kg/cm^2 exerted by a compression molding machine, at 100 °C for 8 min. The films have smooth surface when containing 3 wt% chitosan, while for a higher concentration, of 5 wt% chitosan, they become rough due to phase separation [105]. These blended films have shown nondiffusible antibacterial properties.

Cellulose/xanthan hydrogels have been obtained from different allomorphic forms of cellulose (cellulose I, II, and III) and xanthan, by using epichlorohydrin as cross-linker [101]. The increase in xanthan concentration determined an increase in swelling degree of hydrogels, while using cellulose II led to the highest value of the swelling degree (2146%), which demonstrates the superabsorbent character of these hydrogels. The optical image of the hydrogel reveals a smooth surface and a homogeneous aspect, explained by a good incorporation of cellulose within the xanthan matrix.

Cellulose/lignin hydrogels were prepared in the presence of epichlorohydrin [102]. The color of the hydrogels changes from light to dark brown, as the incorporated lignin amount increases. It appears that the structure is uniform and densely packed (Fig. 7) [106].

Fig. 7 Photo images of CL hydrogels with different compositions: (**a**) CL3, (**b**) CL5. (Reprinted with permission from [106]. Copyright © 2013, Cellulose Chemistry and Technology)

The swelling capacity of these hydrogels increased by increasing lignin content (from 2300 to 3000 wt%). This behavior is explained by the chemical uniqueness of lignin, which contains a high number of polar groups (aromatic and aliphatic hydroxyls, carbonyls, ethers). By involving lignin in cross-linking reactions, some hydroxyl groups are blocked by forming C-O-C linkages, but many other remain free, conferring hydrophilicity to the resulted 3D matrix; thus, pores with different structures and polarities could be formed. An increase in lignin content in cellulose/lignin hydrogels produces a more relaxed network with higher swelling capacity.

Cellulose/sodium alginate hydrogels have also been reported. The introduction of sodium alginate into cellulose hydrogels significantly increases the pore size and swelling ratio of hydrogel samples, while cellulose contributes to enhancing the mechanical properties of the hydrogels. These hydrogels have macroporous structure, excellent mechanical strength, and high equilibrium swelling ratio in water [103].

Bacterial cellulose/gelatin double-network (DN) hydrogels have been synthesized. It was observed that gelatin gel was brittle and easily broken into fragments under a modest compression, while the fracture strength and elastic modulus of a BC/gelatin DN gel were several orders of magnitude higher than those of gelatin gel and almost equivalent to those of articular cartilage. A similar enhancement on the mechanical strength was reported for the combination of bacterial cellulose with other polysaccharides such as sodium alginate, gellan gum, and carrageenan [107].

Bacterial cellulose and gelatin were successfully used to develop a hydrogel composite material [19]. The bacterial cellulose network was filled with gelatin, the glutaraldehyde was employed as a cross-linker, and a malleable and easily shaped at ambient temperature without any external stimuli hydrogel was obtained (Fig. 8).

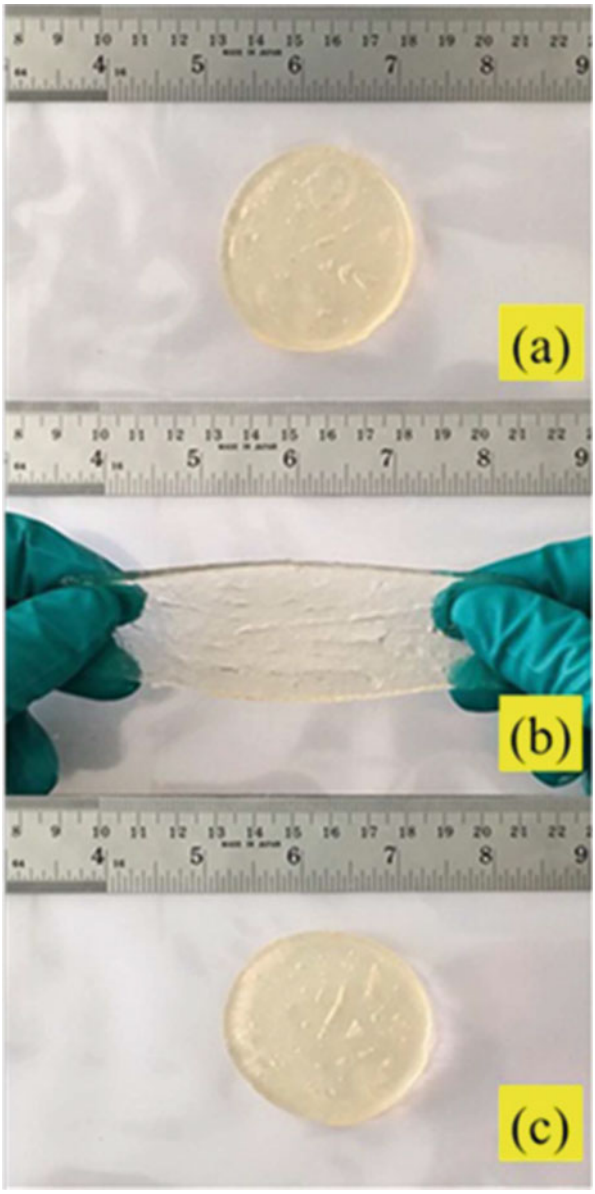

Fig. 8 Photograph of bacterial cellulose-based hydrogel composite (**a**) original form, (**b**) stretchable form, (**c**) reformable form. (Reprinted with permission from [19]. Copyright © 2017, Elsevier.)

The hydrogel composites presented excellent benefits in terms of their thermal stability, chemical resistance, and mechanical properties. Moreover, the swelling ratio of the hydrogel network in water was estimated to be 400–600%.

As many CNC-containing hydrogels target biological or biomedical applications, there has been an increasing amount of research on natural polymer-based hydrogels, primarily based on alginate [108–110], gelatin [111–113], and agarose [114, 115].

Cellulose can also be blended with *synthetic polymers*, such as poly(vinyl alcohol) [116, 117], poly(ethylene glycol) [118], and poly(N-isopropylacrylamide) [119], in order to obtain novel materials for special applications.

Cellulose/PVA hydrogels obtained by physical cross-linking method are of importance for biomedical applications, due to the avoiding of residual amounts of toxic chemical cross-linker and of a higher mechanical strength, higher than that obtained by chemical cross-linking method [116]. The effect of cross-linking methods on structure and properties of cellulose/PVA hydrogels revealed that the chemical cross-linked hydrogels, prepared in the presence of ECH, have a high swelling ratio but low mechanical strength as a result of the weak hydrogen bonding between cellulose and PVA. However, physical hydrogels prepared via solution blending of cellulose and PVA and repeating freezing/thawing cycles exhibit a dense structure between cellulose and PVA, leading to high mechanical strength.

Novel cellulose/PVA hydrogels obtained via physical cross-linking method showed an improved swelling capacity and an increased strength of the hydrogels, due to the presence of cellulose within the 3D network [117]. Moreover, the study regarding the release of vanillin from cellulose/PVA matrices demonstrated an increased percent of bioactive agent released with the increasing of cellulose in the hydrogels and also the shortening of the half time and maximum time of release.

In addition, BC/PVA hydrogels with mechanical properties similar to that of soft tissues have been successfully prepared [120]. Specifically, compositions of the hydrogels that have mechanical properties similar to that of the porcine aorta and the aortic heart valve have been identified. For hydrogel preparation, BC fibers produced by the *Acetobacter xylinum* with an average diameter of 50 nm have been used in combination with PVA and physically cross-linked through freezing/thawing cycles to form biocompatible nanocomposites with good mechanical properties.

CNC/PVA hydrogel showed moderate increases in mechanical properties toward the relatively weak PVA-only hydrogel [121–123]. CNF nanocomposite hydrogels have been used as absorbents due to their relatively high swelling capacity. The macroscopic core-shell hydrogels based on PVA and alginate showed higher storage and shear moduli accompanied by slightly increased dye absorption capacity when CNFs were chemically cross-linked into the core [124].

New hydrogels were prepared from cellulose and poly(N-isopropylacrylamide) (PNIPAAm) with high mechanical strength and adjustable thermosensitivity [119]. The first network was obtained by the chemical cross-linking of cellulose in NaOH/urea aqueous solution, in the presence of epichlorohydrin (ECH), while the second network was prepared by in situ polymerization/cross-linking of N-isopropylacrylamide in cellulose network. The obtained hydrogels exhibit high mechanical strength and adjustable thermosensitivity, which strongly depend on the weight ratio between of both polymer networks.

Thermoresponsive poly(N-isopropylacrylamide) (PNIPAM) polymer networks have also been investigated with CNC fillers, showing characteristic temperature-dependent swelling properties along with tunable mechanics [79, 125]. Yang et al. further demonstrated how CNC surface charge and aspect ratio affected reinforcing

ability in polyacrylamide hydrogels, showing that a higher surface charge density led to better dispersibility, while a higher aspect ratio contributed to increased mechanical properties [126].

Synthetic hydrogels like PEG-based hydrogels have advantages over natural hydrogels, such as the ability for photopolymerization, adjustable mechanical properties, and easy control of scaffold architecture and chemical compositions, but PEG hydrogels alone cannot provide an ideal environment to support cell adhesion and tissue formation due to their bio-inert nature [52, 127].

High-strength cellulose/poly(ethylene glycol) gels have been prepared by swelling cellulose gel membranes in a low-molecular-weight polyethylene glycol (PEG). The cellulose gel membranes have been fabricated by a pre-gelation method through employing cellulose solutions in aqueous NaOH/thiourea at low temperature [66]. These materials exhibit high mechanical performance, and their tensile strength increased sharply from 3.5 to 7.9 MPa with an increase in the molecular weight of PEG from 200 to 800 g/mol [52, 118].

Recently, the ionic interactions between amine-terminated PEG and carboxylated CNFs allow these nanocomposite hydrogels to exhibit a reversible sol-gel transition upon either strain or temperature ramping [79, 128].

6 Factors Affecting the Swelling Capacity of Cellulose-Based Hydrogels

There is little research on the swelling of physical gels due to their weak structure or low swelling, so the majority of the literature is related to the swelling of chemical hydrogels [54].

In order to investigate the *effect of the cross-linking degree on the swelling properties of cellulose hydrogel*, two types of swelling experiments were performed: (i) gels just after synthesis were placed in water, and their volume and weight at equilibrium, i.e., after cellulose complete coagulation, were measured, and (ii) cellulose cryogels swelling in water was recorded (Fig. 9) [59].

The influence of ECH concentration on the swelling degree of cellulose hydrogels (never dried, at equilibrium) showed a dramatic increase up to the maximal value of $Q = 3500\%$ for $R = 1$ and then a decrease at higher R values, reaching $Q \approx 1500\%$. The increase in swelling with the increase of cross-linker concentration is "against" the trends known for classical polymer gels for which the increase in cross-linking leads to the decrease of swelling. The higher the cellulose concentration, the lower the swelling degree of hydrogels, as expected (Fig. 9a). Another interesting point is that with the increase of ECH concentration, samples become more and more transparent: for example, samples prepared with $R = 0$ or $R = 0.25$ are opaque, whereas with $R \geq 2$ they are completely transparent. The transition from opaque to transparent coagulated swollen cellulose stands between $R = 1$ and 2. It may be deduced that the increase of cross-linking thus leads to a more homogeneous structure of coagulated cellulose [59].

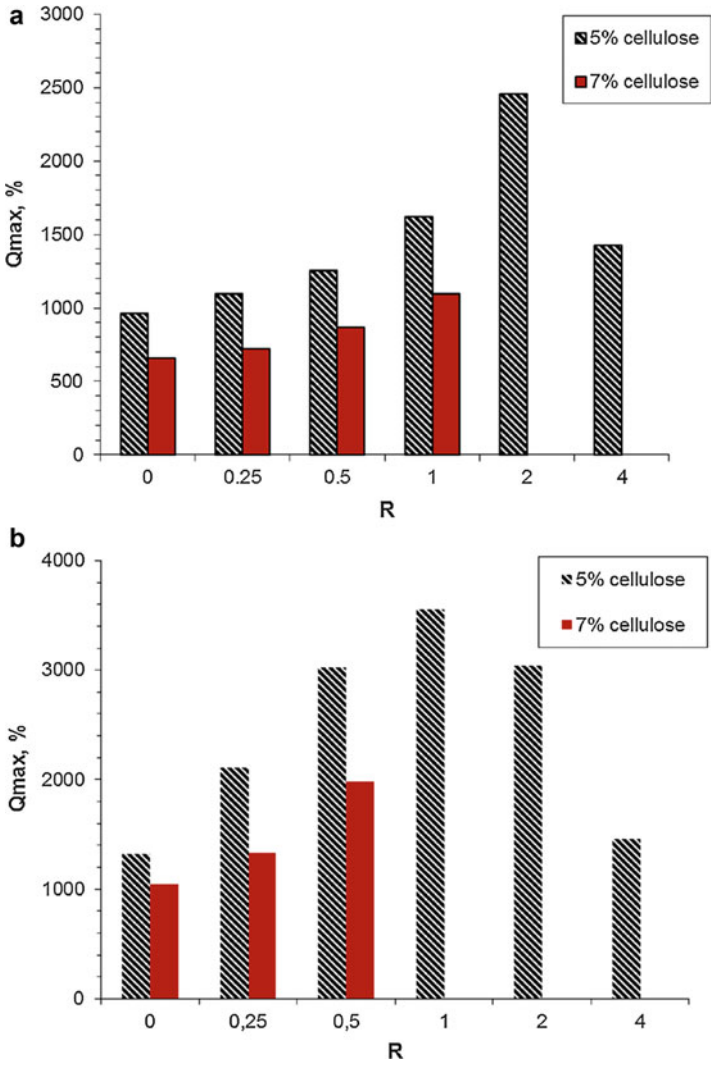

Fig. 9 Swelling degree of (**a**) cellulose hydrogels (never dried, at equilibrium) and (**b**) of cellulose cryogels in water at 37 °C, prepared from 5 to 7 wt% cellulose solutions, as a function of R. (Reprinted with permission from [54]. Copyright © 2017, Elsevier.)

Similar to hydrogels, the degree of swelling of cryogels in water first increases and then decreases with the increase of ECH concentration, for both studied cellulose concentrations (Fig. 10b). However, the absolute values of cryogel swelling are lower: for example, for samples prepared from 5 wt% solution, the minimal swelling of cryogel is around 900% and the maximal is around 2500%, while for hydrogels it is 1300% and 3500%, respectively. Lower swelling of dried compared to never-dried cellulose is due to the well-known hornification phenomenon. What is important is

Fig. 10 Examples of an aquagel and samples after drying with different techniques (aerogel, cryogels, and xerogel) obtained from 7 wt% cellulose solution. (Reprinted with permission from [63]. Copyright © 2016, Springer International Publishing AG.)

that even freeze-dried samples show the "anomalous" swelling, i.e., increase in swelling degree with the increase of ECH concentration, up to a certain value.

It is known that the drying procedure affects the water absorbency capacity of hydrogels. Supercritical or freeze-dried hydrogels retain the microporosity of the gel systems and thus significantly increase the swelling properties compared to air-dried, oven-dried, or vacuum-dried hydrogels, whose capillary retention decreases due to the recrystallization of the biopolymers in the gel systems [54].

However, the morphology of the porous material obtained after lyophilization or supercritical CO_2 drying is very different. While freeze-drying leads to the formation of large pores and channels from several microns to tens of microns, due to the growth of ice crystals, supercritical drying better preserves fine network structure leading to the formation of mesopores and small macropores which is reflected by specific surface area of several hundreds of m^2/g [63, 129–131].

For a systematic study of the *influence of drying method on the morphology and properties of porous cellulose materials*, the "aquagels" obtained after the coagulation in ethanol of cellulose solution in ionic liquid/DMSO mixture, three different drying methods were employed: supercritical CO_2 (aerogels), freeze-drying (cryogels), and vacuum drying (xerogels) (Fig. 10) [63]. Aerogels and both kinds of cryogels are white and opaque, whereas xerogels are yellowish, translucent, and much more shrunk.

Vacuum drying induces strong pore collapse resulting in samples with very low porosity, not-measurable specific surface area, and densities close to that of microcrystalline cellulose. Supercritical CO_2 drying yields nanostructured aerogels with bulk densities between 0.12 and 0.215 g/cm^3 and specific surface area up to 300 m^2/g. Freeze-drying gives highly macroporous cryogels with much lower specific surface areas (at the order of tens of m^2/g), but which can be as light as 0.05 g/cm^3. The difference in the density of aerogels vs. cryogels is due to sample volume contraction during drying step which is more pronounced for aerogels of low cellulose concentrations [63].

The morphology of aerogels is hierarchically structured with pore size varying from few tens of nanometers between the fibrils to few microns between the "hairy" beads. Cryogel morphology is a sheet-like cellulose network with large interconnected pores of several microns. Moreover, it is also possible to vary the pore size within one cryogel sample by applying a unidirectional freezing before

freeze-drying. This allows decreasing pore size in the direction of temperature gradient, from lower to higher temperatures [63].

The pore sizes are affected by the biopolymer concentration, the cross-linking degree, and the drying processes. The pore sizes are generally determined by SEM after lyophilizing (i.e., freeze-drying) the hydrogels, and the resulting cryogels mostly have pore sizes within the average range of 3–8 μm, which decrease with increasing biopolymer concentration and cross-linking degree [54].

In order to establish the *influence of polymer concentration on the average pore size of the hydrogels*, one example that focused on cellulose/lignin (CL) hydrogels was used (Fig. 11) [102]. For CL hydrogel preparation, cellulose was dissolved in NaOH solution at low temperature, it was mixed with different amounts of lignin (CL1, 3:1; CL2, 2:1; CL3, 1:1; CL4, 1:2; CL5, 1:3; as gravimetric ratios), and it was cross-linked in the presence of epichlorohydrin. The SEM micrographs of hydrogels obtained from cellulose (C) and from cellulose/lignin are presented in Fig. 11.

The cross section of the cellulose hydrogels indicates a macroporous structure with an increasing average pore size by increasing lignin content, a fact which suggests that a higher quantity of water can be uptaken. This assumption is in good correlation with the data obtained for swelling degree (Qmax, from 1145% for C hydrogel to 3061% for CL5 hydrogel). An explanation for this behavior is the fact that the incorporation of a higher amount of lignin in the network, owing to a bulky and branched structure, contributes to an increase of ether linkages and implicitly to an increase of the swelling degree of the hydrogels.

Figure 12 clearly evidenced that the hydrogels with a high amount of lignin exhibit a broader pore size distribution than the ones with small quantity of lignin [106].

Thus, it can be concluded that the polymeric ratio significantly influences the average pore size of hydrogels, as well as pore size distribution. By increasing the amount of lignin in the cellulose matrix, the pore size distribution becomes wider, and the share of large pores increases. Such a suggestion confirmed the data obtained from the swelling measurements, showing that the increase of lignin in the CL hydrogels permits a higher water uptake.

Recently, the influence of cellulose concentration on average pore diameter of aero- and cryogels [63] has been studied. For both types of cryogels, the pore size decreases with increasing concentration. For example, the pore size in cellulose cryogel (freeze-dryer) decreases from almost 6 μm to around 1.5 μm when the concentration goes from 3 to 11 wt%; the same trend is observed for prefrozen samples. Overall, using unidirectional pre-freezing and/or varying cellulose concentration allows tuning pore sizes in cellulose cryogels. A similar result, i.e., the decrease of pore size with the increase of cryogel density, was reported for microfibrillated cellulose [132]. Finally, xerogels are, due to strong pores contraction during slow vacuum drying, very dense, and their porosity is close to zero. No macro- or mesopores are visible on SEM images of xerogels [63]. As expected, vacuum drying cannot be used as a drying technique for the preparation of porous non-modified cellulose materials.

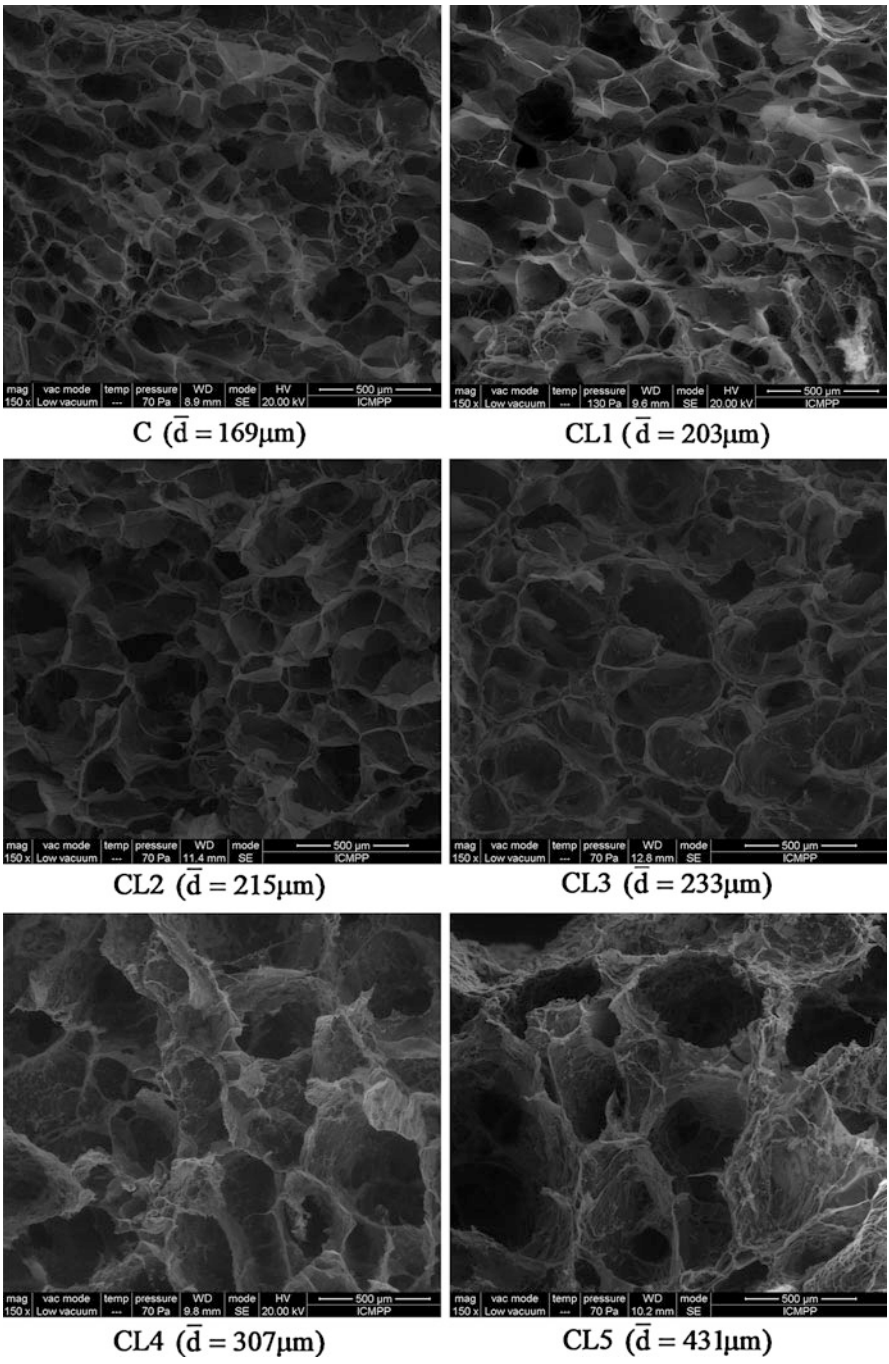

Fig. 11 SEM images of cellulose (C) and cellulose-lignin (CL) hydrogels. (Reprinted with permission from [102]. Copyright © 2012, Elsevier.)

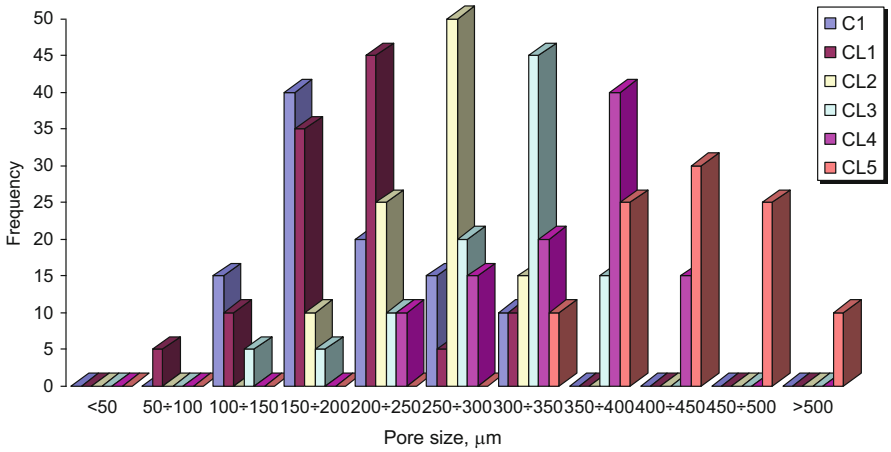

Fig. 12 Pore size distribution of cellulose-lignin hydrogels. (Reprinted with permission from [106]. Copyright © 2013, Cellulose Chemistry and Technology.)

The swelling capacity of the hydrogels and their structural parameters, such as the degree of cross-linking, the average pore size, etc., are important parameters for their biomedical and pharmaceutical applications, i.e., the rate of drug release [133]. Depending on the network nature, chain dissolution may take place along with swelling due to the physical nature of the hydrogel network; thus, drug release results from the complex combination of swelling, diffusion, and erosion mechanisms [51]. When using hydrogels to modulate the drug release, the loading of the drug is performed either after cross-linking or simultaneously, during network formation [134]. Moreover, the bioactive molecule can be covalently or physically linked to the polymer network, to further tune the release rate.

Due to their large water content, hydrogels are highly biocompatible, possess rubbery mechanical properties close to those of soft tissues, and usually allow the incorporation of cells and bioactive molecules during the gelling [51, 135]. Moreover, although cells do not readily attach themselves to highly hydrophilic surfaces, the bulk or surface chemistry of hydrogels can be easily modified with extracellular matrix (ECM) domains, which promote cell adhesion as well as specific cell functions. Hydrogels are thus likely to be ideal platforms for the design of biomimetic scaffolds for tissue regeneration.

7 Applications of Cellulose-Based Hydrogels

Cellulose-based hydrogels are successfully applied to the fields as pharmacy, tissue engineering, and regenerative medicine, due to their unique properties such as hydrophilicity, biodegradability, soft and flexible nature, and biocompatibility. Therefore, cellulose and its derivatives have been used for drug delivery systems,

as well as for burn wound regeneration and cardiac, vascular, neural, cartilage, and bone tissue regeneration:

(a). ***Cellulose I-Based Hydrogels*:** Hydrogels based on bacterial cellulose mimic basic living processes and are of growing importance as bioactive scaffolds, such as skin tissue materials [136], meniscus implant [96], scaffold for chondrocyte proliferation [137], and dental [97]. In medical field, the main applications are wound dressings [138]. Nanoparticles from cellulose I are generated from bacterial cellulose and cellulose from plants. These cellulose nanoparticles were used in drug delivery systems [76, 139], or as scaffolds in artificial ligaments or tendon substitutes, with an excellent cytocompatibility [140]. The formulations from cellulose nanoparticles and silver nanoparticles can be used as microbial medicaments, antibacterial agents in wound dressing, bandages, implants, skins replacements for burnings, face masks, artificial blood vessels, cuffs for nerve surgery, drug delivery, cell carriers and support matrices for enzyme immobilization, cosmetic tissues, etc. [141].

(b). ***Cellulose II-Based Hydrogels*:** The main areas in which cellulose II-based hydrogels are used as biomaterials are in contact lenses [142], wound coverings [143], drug delivery systems [59, 92, 102], and organ and tissue replacements, such as skin, tendon, cartilage, heart valve stents, and bone [54, 139].

8 Conclusions

This chapter emphasizes the recent advances in the design and synthesis of cellulose-based hydrogels. Different methods of cellulose dissolution in common organic solvents, or in novel solvents, such as LiCl/DMAc, NMMO, ILs, and NaOH/urea (or thiourea) aqueous solution, have been reported. A systematic investigation on the physical-chemical properties of the 3D cellulosic networks was done. In addition, the important factors that have an influence on the swelling capacity of cellulose-based hydrogels have been discussed. The large availability of cellulose in nature and its attractive advantages, such as biocompatibility, biodegradability, low cost, and non-toxicity, alongside the possibility to design various formulations of composite hydrogels, meet the demands for many areas of medical applications. A growing interest in the development of bio-nanocomposite structures based on cellulosic materials is expected. In the near future, cellulose-based hydrogels might be ideal platforms for the design of scaffold biomaterials in the field of tissue engineering and regenerative medicine.

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Cellulose Solubility, Gelation, and Absorbency Compared with Designed Synthetic Polymers

4

Robert A. Shanks and Isaac R. M. Pardo

Contents

Abstract

Swelling and solubility of polymers, and in particular cellulose, are controlled by interactions, molecular symmetry, chain flexibility, and order/disorder. Theory is used to explain and predict which liquid systems, polymer structures, and chemical modifications form gels and polymer solutions. Extension of these principles leads to super-absorbent polymers. Cellulose is not water soluble, though some water systems can dissolve cellulose, particularly alkaline or strongly hydrogen-bonding solutions. Less hydrophilic derivatives such as methyl cellulose dissolve in water; while with increasing substitution with methyl groups, cellulose becomes soluble in organic solvents such as dichloromethane. Sometimes temperature can enhance solubility or gelation; alternatively adjusting chemistry through functional group modification to reach an optimum between

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intermolecular versus solvation interactions will create exceptional changes in absorbency. The solvation power can be increased by adding strongly ionic, hydrogen bonding or acid–base solutes such as lithium chloride, urea, or sodium hydroxide. Synthetic polymers have been designed and commercialized with specific solubility, solution rheology, gelation, and absorbency for many applications. Synthetic water-absorptive polymers begin with the choice of monomer(s), molar mass, and chain architecture. Cellulose is separated with exact structure that can be derivatized, grafted, or modified to change its native resistance to super-absorbency, gelation, or dissolving in water. Molecular modeling and simulation are used to evaluate parameters that will describe super-absorbent character. This review explores and evaluates the chemistry and structural symmetry of celluloses and synthetic polymers, leading to solubility, and gelation leading to super-absorbency. Cellulose is emphasized and compared with synthetic polymers where chemistries are designed and created at all levels of structure.

Keywords
Cellulose · Solubility · Absorbent · Gel · Super-hydrophilic · Super-absorbent · Solubility parameter · Interaction parameter · Critical solution temperature

1 Introduction

Super-absorbent polymers must have strong affinity for a solvent or swelling liquid, typically water. The affinity for the liquid must exceed the polymer–polymer affinity. The polymer likely to contain functional groups that interact with the liquid, and they will interact similarly with the polymer either intermolecularly or intramolecularly. A tetramer segment of cellulose is shown in Fig. 1 as a stereo-structure and as a molecular model with charge density surface superimposed and a molecular model with hydrogen bonding highlighted. The latter model illustrates that the surface of cellulose is abundant in hydrogen bond donors and receptors for interaction with other cellulose molecules in crystals and with absorbed water. Intermolecular polymer interactions create parallel sheet-like structures such as found in native (type I) and textile cellulose (type II) [1]. Intramolecular polymer interactions form helical structures, such as exhibited by starch and some proteins. Introduction of chemical irregularities into a structure can limit polymer–polymer interactions and favor interactions with a swelling or dissolving liquid. A divide between dissolving and swelling can be made by crosslinking the polymer, whereby solvent can be absorbed until chains and crosslinks become saturated and at thermodynamic equilibrium. An equilibrium swollen polymer or gel is formed when the solvation force is equal to the force for formation of polymer random coils.

Super-absorbent polymers are exceedingly hydrophilic polymers, which form molecular networks that allow exceptional swelling but prevent dissolving. They may be able to absorb 1000 times their mass of water. Natural substances such as carbohydrates, proteins, and their derivatives feature in this class of material because

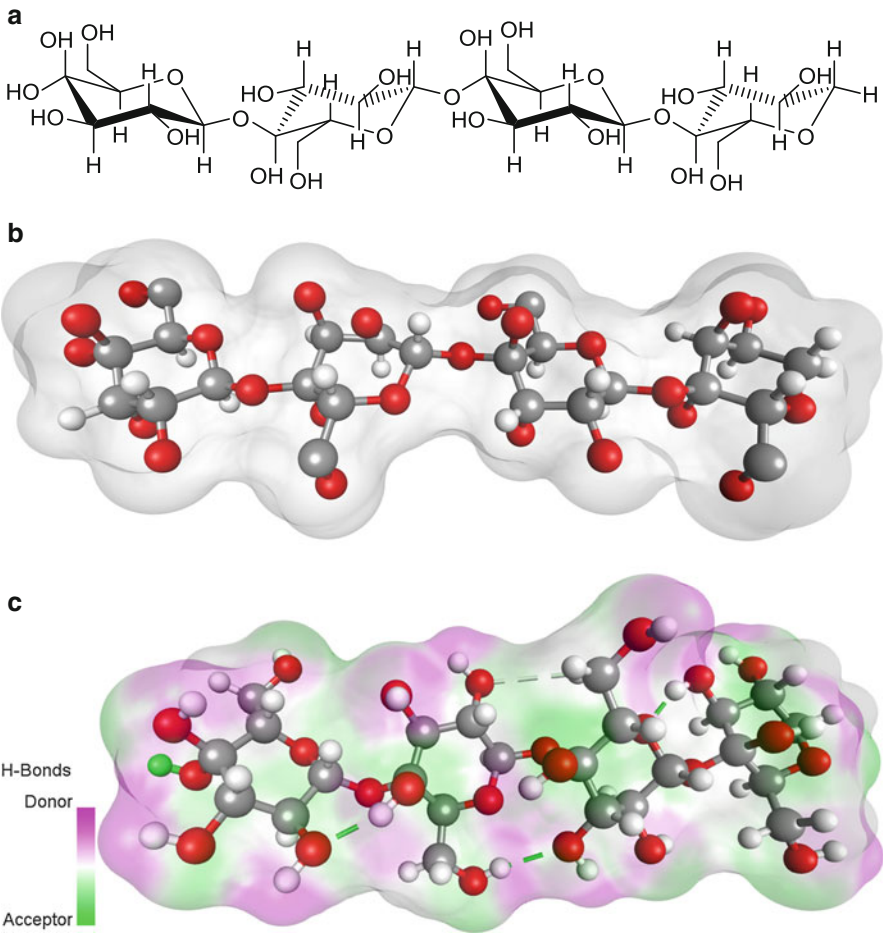


Fig. 1 Molecular structure of cellulose chain segments: (**a**) structure drawing, (**b**) molecular model with total charge density surface, (**c**) molecular model with hydrogen bonding highlighted

most natural species have high water content; water is a necessity for life. There are many synthetic super-hydrophilic polymers that may be based on bio-systems (biomimetic) or principles derived from biomaterials. Solvation principles based on ionic, dipolar, or hydrogen-bonded interactions have been established as an integral part of molecular science. When macromolecules are involved, conformation, packing of chain segments, chain branching, crosslinks, and hydrodynamic volume are additional concepts for solvation. Thermodynamics and kinetics are important for absorption capacity, while absorption rate, desorption rate or hysteresis, gel strength, wicking mechanisms, pH, and ionic sensitivity are additional characteristics. Synthesis and evaluation factors, classified as internal and external factors, of natural and synthetic super-absorbent polymers have been reviewed by Zohuriaan-Mehr and Kabiri [2].

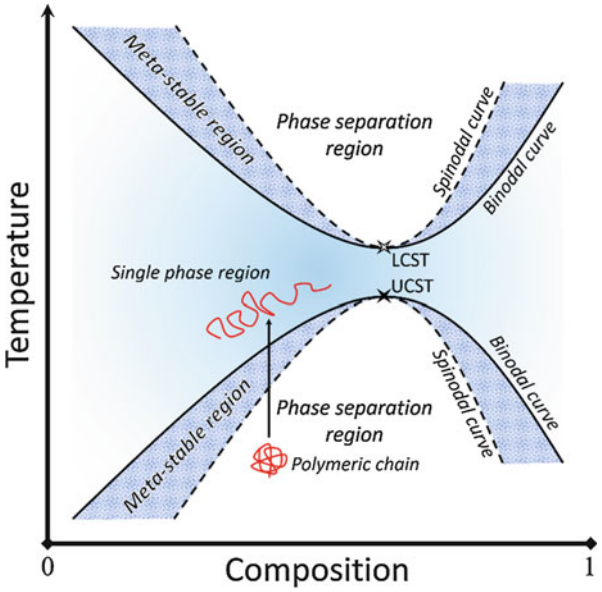
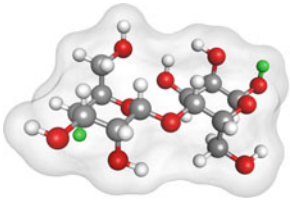
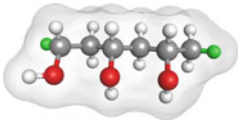
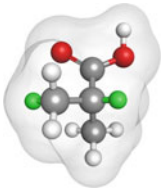
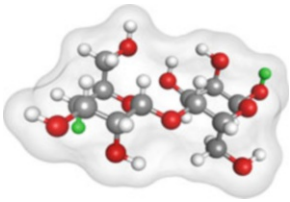
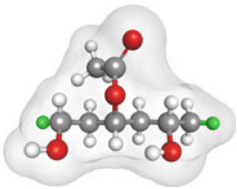
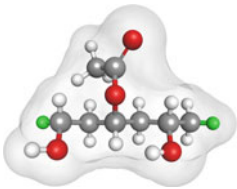
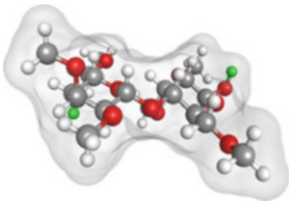
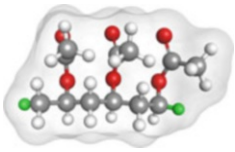
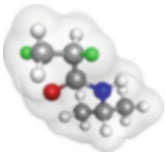


Fig. 2 Schematics of LCST and UCST phase diagram for polymer solutions and blends, showing changes in polymer conformation in one- and two-phase regions

The forces between polymer–polymer, polymer–liquid, and liquid–liquid will all be diminished by increase of thermal energy, or more specifically temperature. Those interactions that decrease most with temperature will determine the nature of the gel or solution. If polymer–polymer interactions decrease most, solvation will increase with temperature, and a lower critical solution temperature (LCST) phase diagram will result (Fig. 2). Solvation and gel formation will increase with temperature. If polymer–liquid interactions decrease most, solvation will be decreased, and polymer solvation and gel formation will reverse upon heating, resulting in an upper critical solution temperature (UCST) phase diagram (Fig. 2). The phase diagram usually shows two boundaries between the separated (two-phase) and solution (one-phase) regions, a coexistence curve (bimodal) for equilibrium phase separation and a stability curve (spinodal) for spontaneous phase separation. The LCST and UCST are the critical points for maximum or minimum temperatures at critical concentrations. Some phase diagrams can combine LCST and UCST behavior when there is an intermediate temperature range within which solubility is favorable.

Other than by thermal changes, polymer–polymer interactions are reduced by decreasing interactive functional groups and/or chain symmetry/regularity. Cellulose is insoluble in water, but monomethyl cellulose is soluble in water and used as a thickening agent, structures shown in Table 1. Replacing some hydroxyl groups with non-hydrogen-bonding methoxy groups reduces inter-cellulose interactions more than it reduced interactions with water, thus allowing water solubility. A synthetic polymer example is poly(vinyl alcohol) (PVAlc). PVAlc is prepared from poly(vinyl acetate) (PVAc), since its virtual monomer, vinyl alcohol, is not stable. PVAc is then hydrolyzed to convert acetate groups to hydroxyl groups. When completely

Table 1 Structures for water-absorptive and water-soluble polymers

Celluloses (monomers)	Poly(vinyl alcohol)	Poly((meth)acrylic)s
 Cellulose	 Poly(vinyl alcohol)	 Poly(methacrylic acid)
 Methyl cellulose	 Poly(vinyl alcohol-co-acetate)	 Poly(hydroxyethyl methacrylate)
 Trimethyl cellulose	 Poly(vinyl acetate)	 Poly(isopropylacrylamide)

hydrolyzed, the pure PVAlc is insoluble because it crystallizes due to symmetry and strong intermolecular hydrogen bonding. When partially hydrolyzed and about 87% hydrolysis seems to be an optimum, with 13% acetate groups remaining, water solubility is optimized. Returning to methyl cellulose, when completed methylated to give trimethyl cellulose, it is water insoluble, but it can be dissolved in polar organic solvents such as dichloromethane. Poly(hydroxyethyl methacrylate) (HEMA) and poly(*N*-isopropylacrylamide) (NIPAM) are much studied polymers with complex interactions with water forming interesting gels, solutions, and phase diagrams.

Another way to increase solubility of polymers is to increase the solvent power. Adding a strong hydrogen-bonding agent to water increased it solvent power. Water–urea mixtures can dissolve cellulose. Acid–base reaction can for salts that are more water soluble so that cellulose is soluble in sodium hydroxide solution. Salt that forms ions in solution increases the solvent power of water, such as lithium chloride solutions that are stronger solvents for highly polar polymers. Sodium chloride and calcium chloride are confirmed to modify water absorption to tapioca starch and contribute anti-plasticization by competing for water with the starch [3].

The consideration of solvation discussed above is about interactions or enthalpy as quantified with solubility parameters, or cohesive energy density, which in a particular polymer–liquid system are equated to the interaction parameter. Entropy is the other thermodynamic parameter that determines solubility or swelling. A swollen or solution polymer becomes less ordered than in the solid and thus gains entropy. The liquid or solvent is even more controlled by entropy because many small liquid molecules that are randomized in the liquid phase lose randomness when they are absorbed into a polymer gel or solvating a polymer in solution. The entropy and interaction parameter concepts are typified by the Flory–Huggins equation (Eq. 1) and the thermodynamic equation defining free energy from enthalpy and entropy (Eq. 2):

$$\frac{\Delta G}{RT} = \frac{\theta_p}{n_p} ln\theta_p + \frac{\theta_s}{n_s} ln\theta_s + \chi\theta_p\theta_s \tag{1}$$

$$\Delta Gm = \Delta Hm - T\Delta Sm \tag{2}$$

where ΔG is the free energy change that must be negative for a spontaneous process such as solubility, χ is the interaction parameter that is a measure on secondary bonding and favors solubility when negative, θ is the volume fraction and n the number of moles of polymer (p) and solvent (s), T is temperature, and R is the gas constant. The entropy (ΔS) is determined by mole fraction and molar volume, the two logarithmic terms in the Flory–Huggins equation. The enthalpy (ΔH) term is a function of interaction parameter and mole fractions of polymer and solvent, the last term in the Flory–Huggins equation. The Flory–Huggins equation is an expanded version of Eq. 2.

This review aims to expand upon these introductory concepts by exploring polymer interactions, solutions, and gels, with emphasis of cellulose and the structures and interactions that lead beyond to super-absorbency. Objectives are to evaluate structure interaction character of synthetic polymers that have been researched or commercialized as super-absorbent materials or solution viscosity modifiers, illustrated in Fig. 3. Molecular modeling and simulation will be applied to evaluate structural, kinetic, and thermodynamic parameters that will typify polymer properties leading to super-absorbent characteristics.

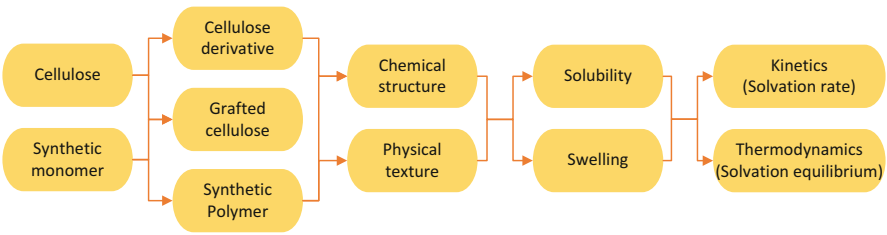


Fig. 3 Review outline, concept, and structure

2 Absorbency, Solubility, and Gelation

Polar polymers absorb and approach equilibrium with atmospheric moisture, that is, humidity. Cellulose and starch typically contain 8–10% water at average humidity of about 50%·RH. Polyamide 6,6 averages 1–2% moisture, and in fiber or thin films, it equilibrates rapidly. The water in polar polymers is a plasticizer. Cellulose fibers become brittle when dried so part of their properties when used as reinforcement in another matrix polymer depends upon their water content, so drying the fibers prior to processing deteriorates composite properties. Starch films are brittle even with equilibrium water content, so they require additional plasticizers such as glycerol, alkyl polyols, poly(vinyl alcohol), and related water-soluble polymers. Water absorption can be increased by destructuring native cellulose and starch with treatments that separate molecules from other components of the natural materials and crystal melting. Melting of these biopolymers means disrupting crystal structure to give an amorphous material, rather than melting in the sense of creating a flowable liquid.

Water absorption causes swelling of polymers in the first instance. Swelling proceeds until polymer–polymer interactions resist further separation of the polymer segments. An extreme of polymer–polymer interactions is chemical bonds or crosslinking where swelling is restricted by the crosslink density. Thermodynamically there are polymer–solvent (water) forces causing absorption, swelling, and potentially dissolving, counteracted by polymer–polymer forces and solvent–solvent forces, combined with loss of entropy or degrees of freedom by the solvating solvent molecules. Poly(2-hydroxyethyl methacrylate) swells to about 36%·w/w of water to form a equilibrium gel that does not proceed further toward dissolving.

Diffusion of liquids and gases through or into polymers displays the same phenomena, though diffusion is typically considered as transport through polymers. Diffusion is the product of solubility and permeability. The diffusing liquid or gas must be soluble in the polymer; this means that the liquid or gas dissolves in the solid to give a solid solution. Additionally, permeability is the transport of liquid or gas across the polymer due to a concentration gradient. Transport through a polymer must be through amorphous regions because any crystalline structures are regular and close-packed, without spaces for foreign molecules. Amorphous regions contain free volume that increases with temperature and expands rapidly at the glass transition temperature (*Tg*). Permeating molecules must pass through a tortuous path that forms by linking of free volumes. Above *Tg* rapid segmental motions create rapidly changing free volume array allowing diffusing molecules to move as free volumes open along their path. Below *Tg* segmental motions are restricted by lack of activation energy, and free volumes become static, preventing diffusing molecules from finding new free volumes for movement. The concentration gradient restricts reverse motion, so the molecules are forced onward. Permeability combined with solubility gives diffusion.

When the polymer–solvent interactions dominate, swelling continues until polymer molecules break from the swollen gel and disperse into a true solution. The separated dissolved polymer molecules adopt a random coil conformation. In a poor solvent, the random coils will be relatively compact because polymer–solvent

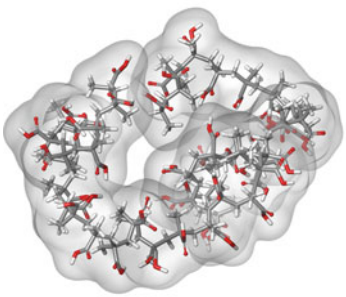
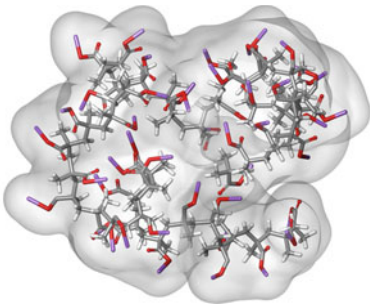
Poly(acrylic acid)		Sodium poly(acrylate)	
			
Connolly Surface		*Connolly Surface*	
Occupied Volume	4279.11 Å ^{3}	Occupied Volume:	5539.94 Å ^{3}
Free Volume:	2157.26 Å ^{3}	Free Volume:	2539.02 Å ^{3}
Surface Area:	1861.88 Å ^{2}	Surface Area:	2179.34 Å ^{2}
Smoothed Solvent Surface		*Smoothed Solvent Surface*	
Occupied Volume:	5760.08 Å ^{3}	Occupied Volume:	7333.26 Å ^{3}
Free Volume:	676.29 Å ^{3}	Free Volume:	745.71 Å ^{3}
Surface Area:	1096.56 Å ^{2}	Surface Area:	1354.94 Å ^{2}
Smoothed Accessible Solvent Surface		*Smoothed Accessible Solvent Surface*	
Occupied Volume:	5760.32 Å ^{3}	Occupied Volume:	7334.42 Å ^{3}
Free Volume:	676.06 Å ^{3}	Free Volume:	744.54 Å ^{3}
Surface Area:	1094.84 Å ^{2}	Surface Area:	1345.50 Å ^{2}

Fig. 4 Random coil comparison of poly(acrylic acid) and sodium polyacrylate

interactions are just sufficient to dissolve the polymer. In a good solvent, the random coils in solution are increasingly expanded. If the polymer chains contain charged groups such as carboxylate anions, repulsions between the charges expand and elongate the random coils. Figure 4 illustrates expansion of random coils by interactions or repulsions according to three different surface criteria calculations based on Connolly surface, smooth solvent surface, and smoothed accessible solvent surface. Sodium poly(acrylate) is shown to expand more than poly(acrylic acid). Poly(acrylic acid) can form intramolecular hydrogen bonds that contract the random coils, while sodium poly(acrylate) has carboxylate anions along the chain that repel and expand the random coils.

Stronger polymer–solvent interactions and more expanded random coils increase solution viscosity. The nature of the polymer is important since apart from the relative interactions, the size of random coils is dependent on molar mass. Branching contributes in that a branched polymer, compared with the same molar mass of linear polymer, will have more compact molecules and hence lower viscosity. An extreme of branching is hyperbranched or dendritic polymers, where the radius of the random coils does not increase as rapidly as the molar mass. With these latter polymers, solution viscosity can decrease with molar mass increase at high molar mass has a reverse effect because molar volume grows more slowly.

Rheology is shear rate-dependent viscosity. If the polymer random coils are separated in solution, they move independently, and viscosity increases linearly (Newtonian) with shear rate. If there are interactions between the random coils, then increasing shear rate is likely to disrupt the interactions, and the viscosity will decrease (shear thinning) with increasing shear rate. If the random coils become elongated at higher shear rates, then the elongated coils exhibit increased interactions thus increasing viscosity (shear thickening) with increasing shear rate. Time delay in returning to equilibrium slow shear rate or static viscosity may be experienced after shear thinning or shear thickening; these delays are thixotropy and rheopectic behaviors, respectively.

Gelation is a discontinuity in the rheology where the substance ceases to flow. There are several definitions depending on the context. With oscillatory rheological measurements performed with a sinusoidal shear frequency in the linear viscoelastic region, gelation is where the elastic response (G′) and the viscous response (G″) are equal. The curves of G′ and G″ cross at gelation because the elastic- or solid-like response becomes greater than the viscous- or liquid-like response. The crossover of the curves may occur with increasing frequency, a time-base response, or with decreasing temperature. Gelation in this context is a result of viscosity reaching a value where the substance is in practice a solid, due to intermolecular interactions. When a substance is undergoing a crosslinking reaction, then gelation is defined by the crosslinks as when crosslinked species extend across the system. Figure 5 illustrates the crossing of G′ and G″ curves that indicates a gel point. The curves

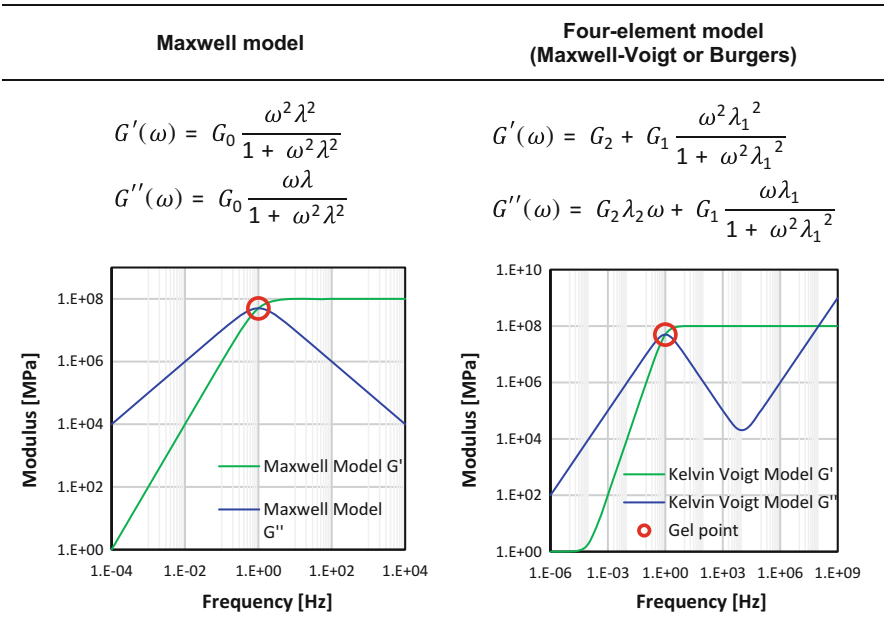


Fig. 5 Complex rheology shear rate curve showing G′, G″ and gel point

were calculated using the Maxwell model and four-element Maxwell–Voigt or Burghers model. A distinction between liquid and solid according to these theories is the relaxation time of the molecules relative to the rate of perturbation.

3 Solubility of Cellulose

Cellulose is not water soluble. As the structural material of plants, it has a configuration enhancing cellulose–cellulose interactions by hydrogen bonding to give two main crystalline forms: native or type I and textile or type II, though other forms are known. Starch has the same chemical structure but opposite configuration about the repeat unit links making it soluble as required for ready metabolism as an energy source. Starch has the linear structure, amylose, like cellulose but with inverted chirality links and a branched structure, amylopectin.

The importance of processing cellulose [4] has resulted in techniques for dissolving it so that regenerated fibers and films can be made. The first technique was complexation with alkaline tetra-ammonia-copper(II), and the cellulose is regenerated by precipitation in acid, such as dilute sulphuric acid. Another route is derivatization using alkaline carbon disulfide to form a soluble sodium xanthate derivative, and the cellulose is again regenerated by precipitation with dilute acid. Cellulose derivatives, crosslinking strategies, and their biodegradability have been reviewed [5], and their response to external physiological stimuli and biodegradability were considered with their use as scaffolding biomaterials, as tissue structures, and in regenerative medicine.

Direct dissolving of cellulose, though not in water, is available using ionic solvents, such as *N*-methyl morpholine *N*-oxide (NMMO). Precipitation of cellulose from NMMO is by extruding the solution into water; after separation of the cellulose, NMMO is recovered for reuse by evaporation of the water due to the high boiling temperature of NMMO. NMMO is used commercially to produce cellulose fibers called Lyocell and Tencel. Other ionic solvents, such as 1-butyl-3-methylimidazolium acetate, have been used to dissolve cellulose. NMMO and ionic solvents have been termed green solvents because they can be purified, dried by evaporating any water, and reused for a new cellulose solution process. Cellulose is regenerated from solution by precipitation into water [6].

Figure 6 shows interactions and phase diagrams for cellulose–water and cellulose–NMMO. The molecular structures reveal hydrogen bond donors and acceptors for the interactions, illustrating the intensity of hydrogen bonds between the species in each case. Calculation indicates a maximum in the free energy of mixing cellulose–water at various temperatures and the energy with molar composition. Cellulose–NMMO exhibits an unexpected minimum in the free energy of mixing with this calculation, which may be indicated by the lower intensity of donor–acceptor sites on the molecular model.

As described above, the configuration of cellulose enhances cellulose–cellulose hydrogen bonding and limits cellulose–water interactions enough to prevent dissolving. The hydroxyl groups on cellulose, particularly the 2-hydroxy, are more

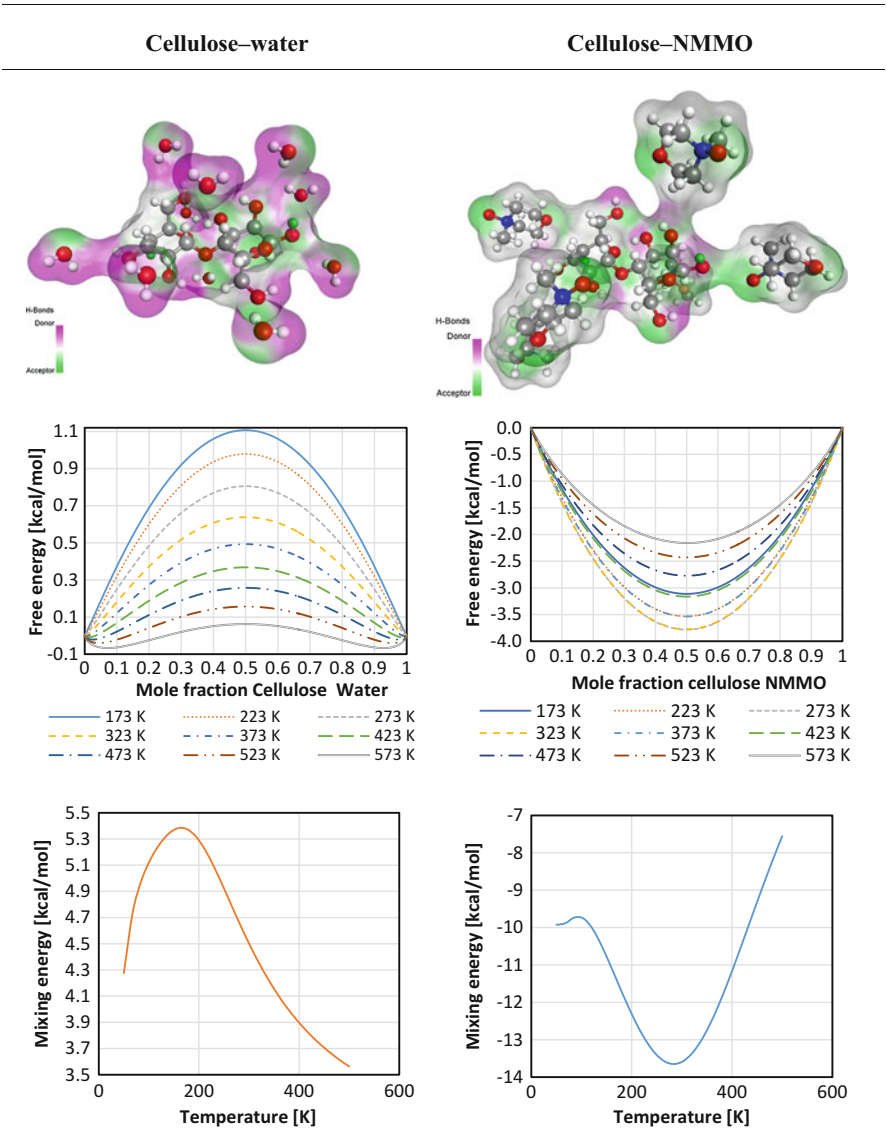


Fig. 6 Cellulose molecular models showing hydrogen-bonding donor and receptors with water (left) and NMMO (right), cellulose solubility predictions in water with UCST, and NMMO with LCST phase diagrams at temperature increments of 50 K from 173 to 573 K; lower curves show the respective mixing energies

acidic than the hydroxyl of a typical alcohol. In sodium hydroxide solution, some sodium salts of cellulose are formed. The sodium salts can accelerate nucleophilic reactions of cellulose, such as formation of methyl, hydroxylalkyl, or carboxymethyl derivatives (see later details of these reactions). The salts facilitate dissolving of

cellulose. Since a lower critical solution temperature (LCST) is involved when dissolving cellulose in sodium hydroxide solution, a suspension of cellulose in sodium hydroxide solution must be cooled. The process involves freeze–thaw cycling, and with each cycle, a small increment of cellulose dissolves. Dissolving cellulose is enhanced with added urea, a strongly hydrogen-bonding agent. Sulphite pulp process-separated cellulose has been dissolved in sodium hydroxide and urea at a low temperature [7]. Hydrogels were prepared from cellulose using water with sodium hydroxide–urea and crosslinking with epichlorohydrin, dissolving the cellulose via heating and freezing cycles [8]. Hydrogels from heating showed macroporous inner structure, while fibrous structures were formed in hydrogels prepared from freezing. Transparency and equilibrium swelling decreased, while re-swelling increased, with cellulose content. Cellulose can be dissolved in aqueous sodium hydroxide–urea, sodium hydroxide–thiourea, and lithium hydroxide–urea at low temperatures and the solutions used to prepare cellulose-based functional materials, such as fibers, films, membranes, microspheres, hydrogels, and cellulose derivatives [9].

4 Super-Hydrophilic Synthetic Polymers

Water-soluble synthetic polymers can serve as a guide for solubility of cellulose and its derivatives. Poly(vinyl alcohol) (PVA) has many –OH group pendant from the chain backbone. The –OH groups can hydrogen bond with water facilitating solubility; however they can hydrogen bond with other PVA segments or molecules detracting from solubility. Pure PVA is semicrystalline due to its symmetric molecules and PVA–PVA hydrogen bonds. If there are some acetate groups remaining from PVA synthesis, then the acetate groups occurring randomly restrict crystallinity and decrease hydrogen bonding, making this type of PVA that has increased water solubility. This occurs with about 10–15% acetate groups. With more acetate groups, solubility decreases and pure poly(vinyl acetate) is completely insoluble in water. The PVA case is analogous to cellulose where –OH groups need to be derivatized to facilitate water solubility.

Poly(acrylic acid) (PAA) is water soluble because of its many –COOH groups that hydrogen bond with water. However, in alkaline (e.g., NaOH) solution, the carboxylate groups become ionized $–COO^{-}\ Na^{+}$, and the anions are more strongly interacted with water. The –COO- groups along the polymer chain repel resulting in uncoiling and hence elongation of the PAA chain, allowing more access for water molecule solvation and much increased viscosity. This is analogous to cellulose methylene carboxylate that is strongly water absorbing and readily water soluble and with high viscosity. Poly(methacrylic acid) (PMAA) is similar to PAA, except that the pendant methyl groups add some hydrophobicity and reduce chain flexibility. PMAA–water interactions are reduced upon heating more than PMAA–PMAA interactions, so heating does not increase solubility; on the contrary, cooling increases solubility. PMAA in water exhibits a LCST, though, while cooling increases solubility, it decreases the rate of solubility. Analogous to cellulose in

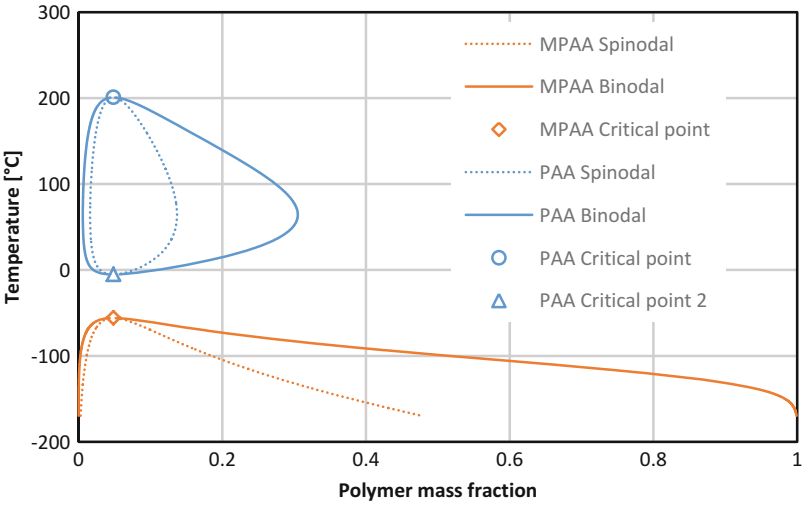


Fig. 7 Composition–temperature phase diagram for poly(acrylic acid) in water

alkaline solutions, PMAA in water is dissolved by freeze–thaw (cool–warm) cycles. A calculated concentration–temperature phase diagram is shown in Fig. 7 including LCST and UCST critical points and binodal and spinodal phase boundaries.

Polyacrylamide (PAM) is a water-soluble polymer or in crosslinked form is used as PAM gels for electrophoresis. PAM gels provide a fixed water phase that allows analyte molecules as large as proteins to migrate under an electrical field. PAM differs from PAA or PMAA in that the polar amide group responsible for solubility can be modified with N-alkyl groups. As the size of the alkyl groups increases, PAM polarity and hence solubility decrease. A critical alkyl group is *N*-isopropyl, *N*-isopropylacrylamide (NIPAM), that exhibits a LCST of 32 °C where the linear polymer becomes insoluble or crosslinked gels shrink considerably. Below LCST hydrogen bonding with water predominates and NIPAM becomes soluble. Concepts relating to NIPAM solubility with its enthalpy of interactions and entropy of movement of water molecules are applicable to cellulose alkyl derivatives.

Polyurethane elastomers are phase-separated materials where the continuous soft phase can be hydrophilic/hydrophobic, depending on structure such as a polyether or polysiloxanediol, and able to expand with water absorption. The urethane segments for a dispersed hard phase function as physical crosslinks and restrains soft phase expansion and hence ultimately solubility [10].

Surfactants display LCST, known as a cloud point. Surfactants are like many water-absorbing or water-dispersible polymers in that they are bipolar with hydrophilic and hydrophobic groups within their molecules. The hydrophobic molecular regions migrate to surfaces, and when all surfaces are saturated, at the critical micelle concentration, they form micelles. When thermal energy disrupts surfactant polar interactions with water, phase separation occurs, and the dispersion becomes cloudy. The cloud point reflects a lower critical solution temperature. Sensitivity of

water–polymer interactions to temperature is an important characteristic of water-absorbing cellulose derivatives, especially as to whether LCST or UCST behavior exists. Enhancement or reversal of water absorbance with temperature can be part of the design of material and products to regulate water content relative to ambient temperatures.

5 Super-Hydrophilic Plants

Super-hydrophilic structures are characterized by their physical surfaces that are in some ways analogous to super-hydrophobic surfaces. Water absorption is facilitated by a low contact angle, typically $<10^{\circ}$. A smooth surface can have increased hydrophilicity if water-absorbing substances are secreted by the plant. Another way is to have high surface porosity giving a larger area over which to absorb water. While convex surface features give high apparent contact angle as in the lotus effect, concave surface features give a low apparent contact angle. Water-absorbing protrusions such as hairs, aerial roots, or sponge-like features are more complex surfaces that increase water absorption rate or create permanent wetness [11]. Super-absorption plant surfaces enhance water and nutrient uptake. Examples are under-water plants and desert plants, the former taking advantage of the environment and the latter surviving in a hostile environment. This description of super-hydrophilic plants concentrates on the surface morphologies that enhance water absorption and retention, as opposed to the chemical structures that attract water.

6 Super-Hydrophilic Cellulose

Cellulose solubility in water is facilitated by reducing hydrogen-bonding groups. This may seem contrary to expectation; however alkylation, particularly methylation, reduces cellulose–cellulose hydrogen bonding, and the alkyl substituent reduces cellulose regularity and ability to pack into crystals. Monomethyl cellulose is water soluble, forming highly viscose solutions. It is used as a thickening agent in many water-based consumer products. Adding further methyl groups reduces hydrogen-bonding capacity further and prevents water solubility. Trimethyl cellulose becomes soluble in polar organic solvents such as dichloromethane. The water solubility of monomethyl cellulose provides a guide for other derivatives to give water solubility.

Reduction of cellulose chain regularity and hence cellulose–cellulose hydrogen bonding can be achieved by using hydrogen-bonding alkyl derivatives. Reaction with propane-1,2-oxide gives hydroxypropyl cellulose with substitution mainly on the more nucleophilic 2-hydroxy position. Hydroxyethyl cellulose can be prepared by reaction with ethylene oxide, though this reaction is less convenient because ethylene oxide is a gas. Structures for hydroxyethyl and hydroxypropyl cellulose are shown in Fig. 8. These cellulose derivatives, together with carboxymethyl cellulose form the basis of cellulose hydrogels, in conjunction with blends with synthetic

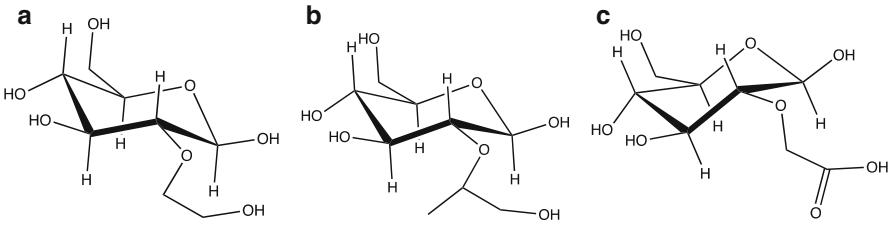


Fig. 8 Water-absorptive and water-soluble cellulose derivatives: (**a**) hydroxyethyl cellulose and (**b**) hydroxypropyl cellulose, (**c**) carboxymethyl cellulose

polymers and polyelectrolyte complexes. Cellulose–inorganic hybrid hydrogels are prepared by dispersing inorganic nanoparticles in a cellulose matrix [12].

Substitution with chloroacetic acid is a nucleophilic reaction that forms the acidic derivative carboxymethyl cellulose (CMC), structure shown in Fig. 8. CMC is soluble in water. In alkaline solution of sodium hydroxide, the sodium salt is formed. Sodium cellulose methylene carboxylate has a negative charge on each substitution. The negative charges reduced cellulose–cellulose interactions by mutual repulsions while increasing interactions with water. Sodium salts are known to be soluble in water, and CMC is no exception; however the repulsions between cellulose chains extend random coils imbibing more water and causing extremely high viscosity to the point of gelation.

Carboxymethyl cellulose has been crosslinked to cellulose using epichlorohydrin in a water solution containing sodium hydroxide and urea [13]. Urea is a hydrogen-bonding additive to assist dissolving cellulose in water, while sodium hydroxide is a base catalyst for the nucleophilic reaction with epichlorohydrin. CMC provided the water affinity and porosity, while cellulose provided structure and strength to the water-swollen gels. Swelling was dependent on CMC content, and swelling diminished with salt concentration in the water.

An extension of cellulose derivatization is formation of graft copolymers between cellulose and another synthetic polymer. With a grafted polymer, the substituent becomes a polymer rather than a single organic group. Grafting is classified as grafting to or grafting from depending on whether the initiating site is on cellulose or the monomer/polymer graft. An example of chain growth grafting from cellulose is the ring-opening reaction with caprolactone. Base catalysis creates an initiating alkoxide from a hydroxyl on cellulose, predominantly the more acidic 2-hydroxy. The alkoxide initiates a nucleophilic ring opening of caprolactone that proceeds with other caprolactone monomers. Radical initiation is induced by redox catalysts such as cerium and peroxide. An oxy-radical is formed that propagates polymerization of styrene, acrylonitrile, and (meth)acrylates including esters or carboxylic acids. The latter carboxylic acids lead to increased water absorbance, while other monomers increase water resistance of cellulose. Cellulose sourced from wheat straw has been grafted with acrylic acid or acrylamide using redox initiation in water with N,N′-methylenebisacrylamide as crosslinker, to obtain materials with up to 134%·w/w water absorbency and 44%·w/w water absorbency in 0.9%·w/w

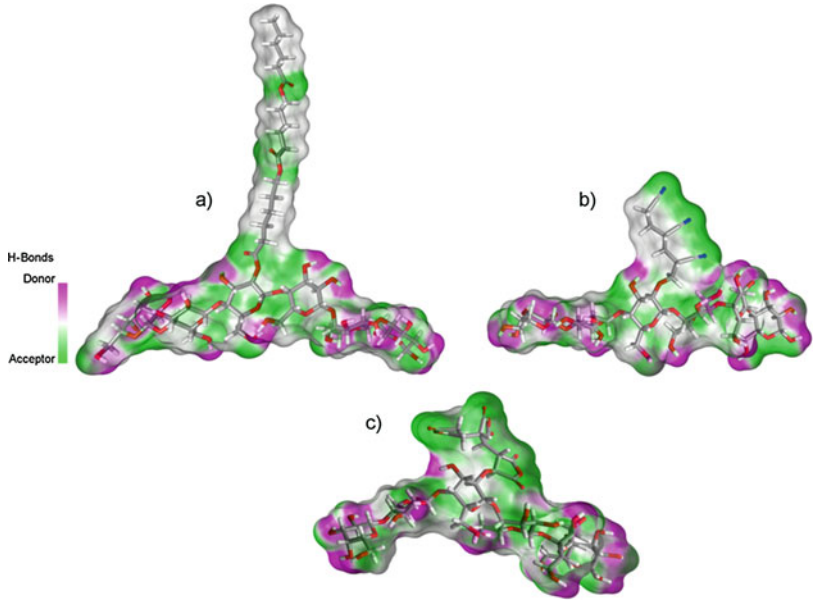


Fig. 9 Grafted cellulose structures with (**a**) caprolactone, (**b**) acrylonitrile, and (**c**) maleic anhydride

sodium chloride solution [14]. Nanocomposite hydrogels have been prepared from carboxymethyl cellulose grafted and crosslinked with methacrylic acid to enhance permeability and drug release. Composition was optimized for swelling and gel strength [15].

Step growth grafting from cellulose can proceed from esterification using maleic anhydride, succinic anhydride, or alkyl succinic anhydrides, linking with diols, glycerol, or formation of some crosslinks within/between cellulose. Cotton cellulose was grafted with succinic anhydride using 4-dimethylaminopyridine as catalyst in solution with lithium chloride and *N*-methyl-2-pyrrolidinone or tetrabutylammonium fluoride and dimethyl sulfoxide. The hydrogels absorbed 400 times by mass of water and functioned adequately in water containing sodium chloride, and they were biodegradable [16].

Figure 9 shows some molecular models of cellulose grafted with caprolactone, acrylonitrile [17], and maleic anhydride. The grafted species may form as compatibilizers for blended polymers or form dispersed phase morphologies within the starch; their resistance to separation is assured by the linking chemical grafts.

Grafting to cellulose can be via the epoxy reaction with cellulose hydroxyls. Typical epoxy resins can be used or copolymer containing epoxide such as poly (ethylene-*co*-glycidyl methacrylate). Another facile grafting to or from reaction is the urethane reaction. An isocyanate-terminated polymer can react with cellulose hydroxyl to form a linking urethane group. Hydroxyl groups undergo many reactions, and those of cellulose being more acidic than typical alcohol hydroxyls are able to participate with advantage in these reactions. A practical problem with

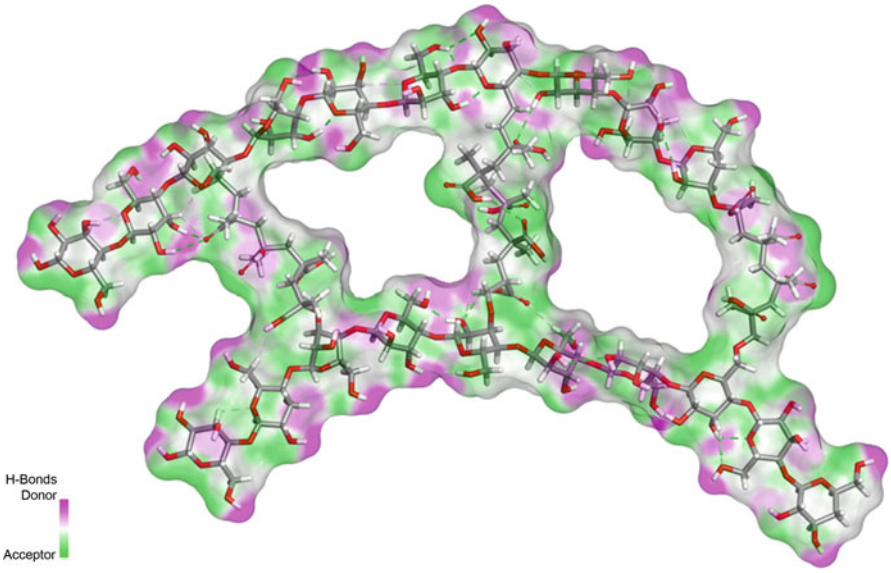


Fig. 10 Grafting and/or crosslinking via epoxy or urethane reactions

performing graft-to reactions is the mutual miscibility or solubility in a mutual solvent since reactions are inefficient when the two reactants are immiscible or incompatible. Some reactions can be performed via reactive extrusion, such as between cellulose dispersed in poly(ethylene-*co*-glycidyl methacrylate) or polypropylene-*graft*-maleic anhydride. Figure 10 shows some schematics of cellulose together with grafted species that may found intermingled or laminar supramolecular structures.

This comparison section is concluded with starch, another hydrophilic natural polymer. Starch differs from cellulose in two structural features. The main distinction is linking of glucose units via alpha-1,4-acetals in starch instead of beta-1,4-acetals in cellulose. This single change in stereochemistry is amplified by the repeating links that may typically be 3000 in cellulose. The alpha links form a helical structure instead of the planar structure that allows close stacking in cellulose. The alpha links create a dihedral bend at each link forming a coil over several links. Thus starch forms an open helical structure that can accommodate absorbed molecules within helices or between helices. Because of this stereochemical difference, starch is more water absorptive and soluble compared with cellulose. Starch with alpha-1,4- links is amylose, a linear molecule similar to cellulose. Another form of starch, amylopectin, contains a small proportion of 1,6-links, where each of these links forms a chain branch. Amylopectin has many branches in each of its very large molecules.

Figure 11 shows amylose and amylopectin chain segments that have partially coiled with energy minimization and molecular dynamics. The bond structure is surrounded by an electron density surface to portray the shape of the molecule. Both

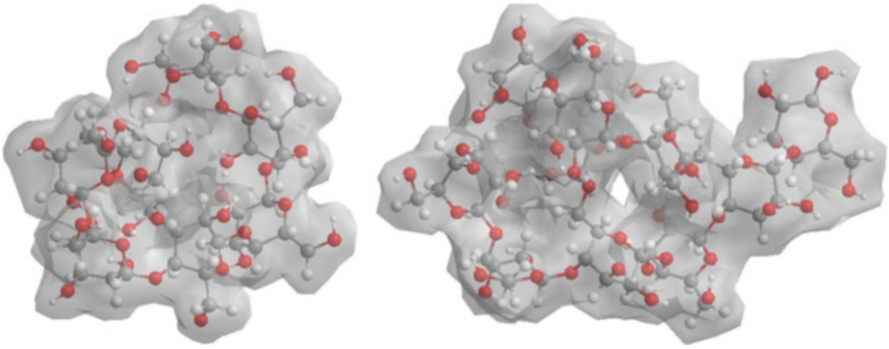


Fig. 11 Starch molecular model showing linear (left), branched (right), and coiling (both)

molecules show an initial inner channel formed by the helical molecules, which for longer chain segments can entrain other molecules such as iodine and stearic acid. Calculation of the electron density surfaces reveals capability as hydrogen bond donors or acceptors in amylose and amylopectin. The electron density surfaces illustrate the ability of starch to absorb and interact with water and other highly polar substances, such as glycerol. Starch interactions with hydrophilic plasticizers such as glycerol and xylitol, in conjunction with water, were shown to limit retrogradation and decrease the glass transition temperature [18]. An anti-plasticizer action was observed for each plasticizer over concentration ranges, which was due to plasticizer–water interactions replacing interactions of both with starch. Xanthan gum and other carbohydrates are strongly water absorptive and may dissolve in water to give highly viscous solutions. Crosslinked gums plasticized with sugars, glycerol, or glycols can be combined with starch to give flexible films with large elongation at break and high water content [19].

Chitosan is closely related to cellulose with the 2-hydroxyl on each glucose monomer unit replaced by an amino group. Chitosan-*g*-poly(acrylic acid)–montmorillonite has been prepared as a super-absorbent nanocomposite, with pH-dependent response [20].

Comparison with synthetic segmented polymers, and trends in behavior described in polymer science theory, is the observation and prediction that branched polymers tend to be less crystalline because branches are an irregularity that inhibits crystallinity and that branched polymers tend to be more soluble than linear polymers of the same chemical structure. Native starches reverse this concept because the branched amylopectin is crystalline while the linear amylose is amorphous. When added to water, it is the linear amylose that is more soluble than the branched amylopectin. Natural polymers or biopolymers and synthetic polymers are sourced or synthesized differently, yet all polymers must conform to the same structure–property relationships that have been established as the basis of polymer science. Fortunately, this chapter is about cellulose, so I can leave it to the reader to consider this contradiction between amylose, amylopectin, and other linear and branched polymers.

7 Comparison Polymers–Super-Absorbent Polymer (SAP) Gel Particles

Poly(hydroxymethyl acrylate) (HEMA) is a water-absorbing polymer used in soft contact lenses. Figure 12 shows polyHEMA segments with associated water molecules and a self-replicating cell containing several polyHEMA chains and absorbed water molecules. It forms a gel upon absorbing about 36%·w/w water; at this water concentration, it reaches equilibrium giving suitable softness, strength, and water content for oxygen transmission for comfort and eye health. From HEMA structure, it could be thought that it should be soluble in water; however water is absorbed, and the HEMA swells until the equilibrium water concentration when polymer–polymer interactions, hydrogen bonds, limit further swelling. Another factor in the equilibrium is the water–HEMA interactions, and the negative contribution of decreased water entropy as bound water has less degrees of freedom than free water. Another possibility is that there is some transesterification in HEMA leading to formation of some ethylene dimethacrylate and methacrylic acid, where the former is a tetrafunctional crosslinking monomer.

Crosslinked poly(acrylic acid) and polyacrylamide have structures where random sequences of the two monomers decrease regularity for polymer–polymer and more water came be absorbed without dissolving the polymer because it is slightly crosslinked. Crosslinking density must be lost to just prevent dissolving while allowing extensive swelling. This copolymer is a typical super-absorptive example that can absorb many times its own mass of water. Increasing pH to form carboxylate salts of the poly(acrylic acid) units further increases water absorption by increased water interactions and expanding the swelling by negative charge repulsions along the macromolecules.

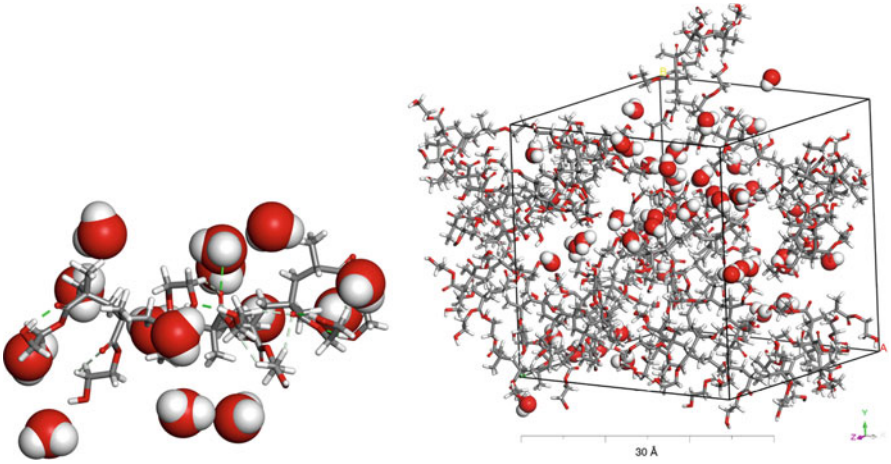


Fig. 12 Molecular model of hydrated poly(hydroxyethyl methacrylate), left, chain segments with absorbed water molecules showing hydrogen bonds; right, a cell containing multiple polyHEMA chains with absorbed water molecules

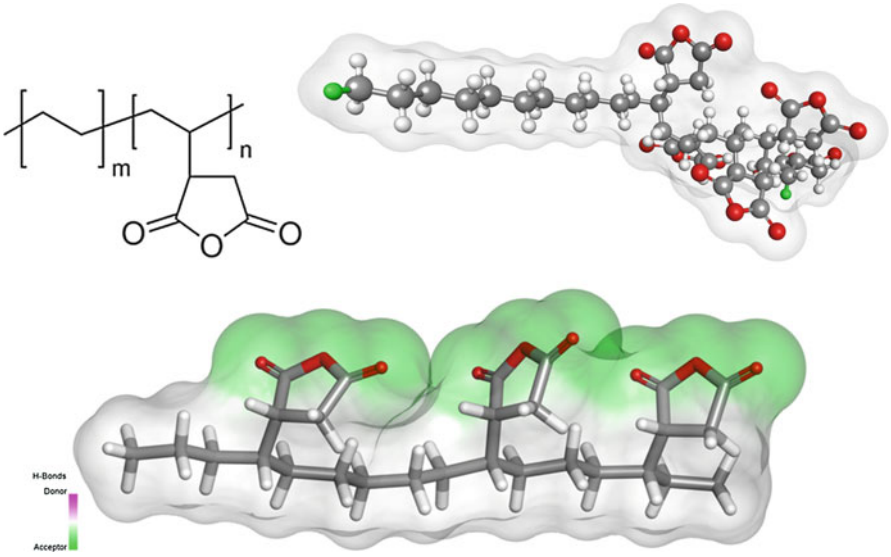


Fig. 13 Molecular structure and models of poly(ethylene-g-maleic anhydride) segment, top, structure and model; lower, model with hydrogen-bonding donors shown

Poly(ethylene-*co*-maleic anhydride) (Fig. 13) is contrasted to the former copolymer in that the ethylene units are hydrophobic while the maleic anhydride units, which are converted into two carboxylic acids when in water, have double carboxylic acid functionality. The reactivity of maleic anhydride, a 1,2-disubstituted alkene, is such that it will not homopolymerize, so each maleic anhydride chain unit will be preceded and followed by an ethylene. While the ethylene units are hydrophobic, they give weak polymer–polymer interactions and reduced regularity within polymer chains allowing random coils to readily swell with absorbed water clustered about the maleate units. When pH is increased and the maleate units, such as dicarboxylates, become salts, water is strongly attracted. This balance of water attraction and polymer–polymer repulsions from the anions and assisted by weak easily disrupted interactions from the ethylene hydrophobic groups is favorable for both sides of the equilibrium equation, resulting in a water super-absorptive polymer.

Sodium acrylic acid-vinyl alcohol copolymer has both monomers with polarity and hydrogen-bonding capacity. Hydrogen bonding within the copolymer chains should cause tight random coils. Water absorption and solubility are likely to occur with this copolymer. Crosslinking should be included to prevent solubility, using a small amount of a diacrylate ester. The pH can be increased to introduce carboxylate anions, again causing ionic repulsions within the polymer and expanding random coils while water will be strongly absorbed forming a super-absorptive gel.

Cationic polymers can be super-absorbents, as well as the more prevalent anionic polymers. Copolymerization of *N*,*N*-diallyl or *N*,*N*-dimethyl ammonium chloride with *N*-vinyl 2-pyrrolidone in the presence of *N*,*N*,*N*′,*N*′-tetraallyl piperazinium

dichloride as crosslinker has been used to prepare cationic water absorbents with the cationic monomers being separated by N-vinyl 2-pyrrolidone units [21]. Typically, 0.5% crosslinking gave the highest swelling ratio of 360 times the mass of water when only the cationic monomer was present. Cationic quaternary ammonium polymers have an advantage of being antibacterial. As for anionic water absorbents, the cationic types are susceptible to ionic strength in absorbing water.

Cationic nano-fibrillated cellulose was prepared by etherification with quaternary ammonium compounds, and they exhibited broad-spectrum antimicrobial activity that was proportional to the extent of etherification. Cationized nano-fibrillated cellulose showed cytotoxicity with human cells, enabling the manufacture of safe, insoluble, and permanently antimicrobial materials by an aqueous synthesis [22].

The examples discussed of polyelectrolyte gels demonstrate the principles for achieving facile swelling with strong attraction and hence absorption of water. The anionic carboxylate gels can be extended to zwitterionic gels provided that regularity is disturbed so that positive and negative species do not associate but are open to hydrogen bonding with water, hence facilitating water absorption.

Combinations of natural polymers with synthetic polymer grafts have been discussed. To conclude this section, a further example of graft-polymerizing acrylamide (AM) onto potato starch is presented. Starch is not sufficiently water attractive or soluble to form a super-absorptive polymer alone. When acrylamide is grafted from starch and some bis-acrylamide monomer is added for crosslinking, then water absorption can be adjusted by composition to give water super-absorption; similarly with grafts of acrylic acid and methacrylic acid. These three monomers are water soluble so grafting can be performed in a water solution of starch and a monomer together with a redox initiator. Functional group reactions with isocyanate have been used to form starch–polyurethane grafted hybrids that decrease solubility of films prepared from the starch [23].

8 Kinetics and Equilibria

Water absorption with swelling occurs until there is a balance of free energy due to interactions between each of the components and entropy of the system. This is a thermodynamic equilibrium that is described by the Flory–Huggins equation (Eq. 1) through temperature, molar volumes, and the interaction parameter. Flory–Huggins is much cited because it presents a high-level, lattice-confined overview of the complex and diverse interactions between polymers and liquids. Atomistic molecular models use the Flory–Huggins concepts with constraint of a lattice and with a temperature-dependent interaction parameter based upon all interactions quantified by a validated force field. The equilibrium state of a hydrated polymer gel does not consider time, that is, the kinetics of absorption and desorption (Fig. 14).

Kinetics is the temperature-dependent rate of absorption of water; in addition to solubility is diffusion rate that is often described by the Fick Law. It is likely that the absorption rate will differ from the desorption rate giving a sorption hysteresis. It might be desirable to have rapid absorption of water so that a swollen gel would form

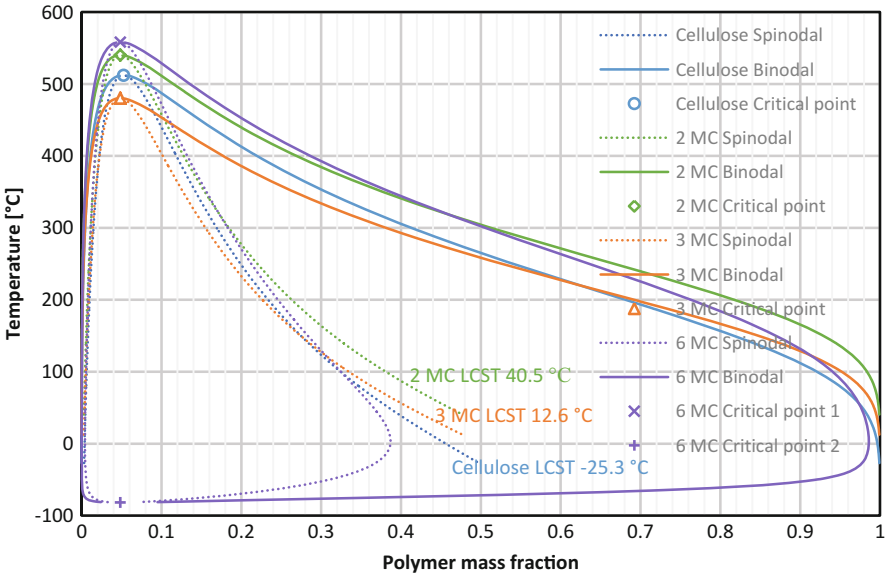


Fig. 14 Molecular model simulated temperature–composition phase diagram for polymer water

rapidly or if a product was designed to contain water spillages that rapid absorption would be preferred. Water-release processes of pre-wetted super-absorbent polymer particles can be slow, so that entrained water would be slowly released, such as over a week, while the water was being released to soil for plants to be grown under constant hydration.

Super-absorptive polymers solvate and bind with water strongly. Water desorption will be resisted both kinetically as observed as hysteresis and thermodynamically since the binding free energy must be overcome by more favorable state for the water. Desorption will be kinetically favored by a low concentration of water, dry conditions, external to the super-absorption polymer gel environment.

9 Applications

Slow release of water to soil for plant growth between watering cycles is important for agriculture and horticulture applications, as mentioned in the previous example. Super-hydrophilic polymers are used in agriculture for water retention on rocky slopes, eco-engineering, soil's water-holding capability, seed germination rate, plant survival, and soil erosion containment [24].

Medical and physiological applications are for wound dressing with included antibacterial agent, especially in the case of burns where an artificial skin is required, controlled release gels, and hot and cold therapy packs. Hydroxyethyl methyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose are used in

eye drops, artificial tears, contact lens fluid, cosmetics, adhesives, and excipient/tableting ingredient. Polysaccharide nanoparticle gels for vaccine delivery and treatment of viral or bacterial infections have been described [25]. Tocopheryl acetate has been released from maize starch granules and structural properties; particularly free volume of the macromolecular network was related to release kinetics [26].

Super-absorptive polymers are coated onto or extruded into fibers, yarns, and textiles. These products are used for water blocking, filtration, hygiene, apparel, cable, and related products. Examples include Ultrabloc for dry blocking cables requiring water blocking for fiber optic cables, copper cables, and high-voltage energy cables. Ultrabloc is a spun super-absorbent polymer yarn with a polyester wrap. Another water-blocking and absorbing yarn is Swellcoat. Technical Absorbents manufacture a super-absorbent water-blocking yarn that can be incorporated into cables; it will rapidly absorb liquid from a damaged region and swell to form a gel, blocking any further water ingress. Technical Absorbents can be used for moisture management in garments to transport moisture away from the skin to the garment. Several fabrics for disposable and washable apparel are based on evaporative cooling and wicking. These fabrics create optimum conditions to increase wearer comfort next to the skin and over outer clothing. Star Materials supply fast water-absorbing and high tensile strength yarn, used in communication and optical, power, or marine cables for binding, tightening, and prevention of water penetration.

Swelling controlled by changes in environment, such as acid/base, electrical field, termed smart swelling, can be used for controllable delivery and food packaging. As thickeners and emulsifiers, methyl cellulose will set while hot and liquefy while cold; carboxymethyl cellulose, often as the sodium salt, is used in foods, paint and adhesives as a thickener, in ice-cream to prevent water–ice crystallization, and as an emulsion stabilizer for foods and toothpaste.

Fig. 15 shows the expansion of crosslinked super-absorbent polymers from particles to spheres to enlarged spheres. Expansion occurs until the extended chain segments between crosslinks reach equilibrium with the solvation force of the absorbing water. Pure water typically gives optimal expansion compared with water containing dissolved salts. The water may contain other substances such as nutrients for release to plants or pharmaceuticals for release to assist adjacent tissue healing.

These applications are selected examples since controlling the properties, storage, and delivery of water is a diverse field that includes many materials, with polymers and particularly super-absorptive polymers being substantial contributors.

10 Conclusions

Polymer regularity, polymer–polymer interactions, polymer–liquid interactions, and system entropy have been demonstrated to determine liquid absorbance and solubility. When a polymer is crosslinked, either through chemical bonds or physical interactions, then solubility is prevented, and water absorption is limited by the crosslink density. Super-hydrophilic polymers must be strongly water absorbing

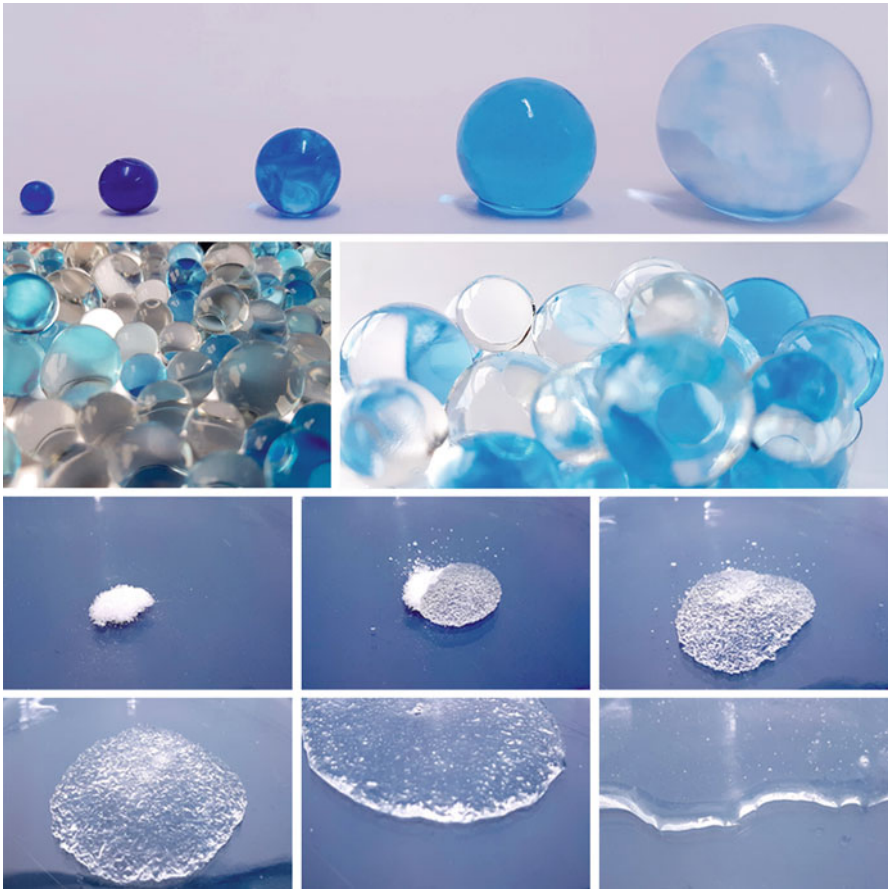


Fig. 15 Images of products using super-absorptive polymers: (top) swelling of polymer beads, (middle) swollen polymer beads, and (lower) swollen polymer particles, white granules, progressively forming a gel as water is added

such that they would dissolve were it not for crosslinks. The interactions thermodynamically contribute to the enthalpy of solvation. Another important thermodynamic factor is the entropy of solvation that is significantly caused by constraints on degrees of freedom of strongly absorbed, hydrogen-bonded water molecules. Enthalpy and entropy combine to give the free energy of solvation that must be negative for spontaneous water absorption. The kinetics of water absorption and any absorption–desorption hysteresis contributes to applications of super-absorbing polymers. Even though a large fraction of water can be absorbed, the time to reach equilibrium must be suitable. Rapid absorption kinetics are favored by surface wetting and porosity, to facilitate diffusion. Cellulose is not sufficiently polar and too regular to be a super-absorbent polymer. Functionalization to form carboxymethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, and

methyl cellulose increases polarity and decreases packing ability of cellulose. Other grafting monomers such as acrylic acid, methacrylic acid, acrylamide, and maleic anhydride increase polarity, and as polymeric grafts, they prevent ordered cellulose structures. Applications of super-hydrophilic cellulose derivatives include water absorption in sanitary products, water and nutrient release in agriculture, and antiseptic hydration materials for wounds and physiological treatments. Since these hydrated materials contain extremely large proportions of water, they can be considered as a means of storing and delivering quantities of solid water.

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Review of the Mechanistic Roles of Nanocellulose, Cellulosic Fibers, and Hydrophilic Cellulose Derivatives in Cellulose-Based Absorbents

5

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Contents

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Abstract

Cellulose – either in solid form or as a highly hydrophilic chemical derivative of cellulose – can serve multiple and synergistic roles in the preparation of absorbent materials to meet the requirements of diverse absorbent products. Progress in the preparation of nanocellulose products, including nanocrystalline cellulose (CNC), nanofibrillated cellulose (NFC), and bacterial cellulose (BC), is opening up new possibilities for the reinforcement of hydrogels. Conventional cellulosic fibers, including kraft pulp fibers (e.g., fluff pulp), mechanically pulped lignocellulosic fibers, and recycled paper fibers can provide a structure to fine-tune the mechanical and drainage properties of products that can include superabsorbent materials. Carboxymethylcellulose (CMC) is an especially strong candidate for preparation of the swellable phase of a hydrogel. The high content of carboxylic acid groups in CMC gives rise to a strong swelling tendency, especially at neutral to alkaline pH values. The uptake of water can be understood based on concepts of osmotic pressure, in addition to any salinity in the fluid that is being absorbed. The swelling can be adjusted by the choice and amount of a cross-linking agent. Notably, some of the needed cross-linking effect can be optionally provided by nanocellulose or conventional cellulosic fibers. Combinations of solid cellulose entities and water-soluble cellulose-based polyelectrolytes can be used to prepare completely bio-based products that offer an alternative to the presently available disposable absorbents, which are based mainly on petroleum-based superabsorbent hydrogels. Chemical and physical aspects of cellulose and its derivatives also help determine what happens during drying of absorbent products; some swelling ability may be lost irreversibly due to highly organized hydrogen bonding and coalescence of the cellulose-based macromolecular chains. Since cellulose can be involved in both the structural and chemical aspects of highly absorbent products, there will be unique mechanistic roles governing water uptake, water holding, and even the environmental impacts of cellulose-based absorbent products.

Keywords

Hydrogel · Carboxymethylcellulose (CMC) · Osmotic swelling · Cross-linking · Biodegradable · Nanofibrillated cellulose (NFC) · Cellulose nanocrystals (CNCs)

1 Introduction

The goal of this chapter is to review the main mechanisms by which cellulose and its derivatives can participate in highly water-absorbent products. A key challenge lies in the fact that cellulose itself – either in its native form or after conventional isolation methods – is merely absorbent, but not highly or "super"-absorbent. To qualify as a superabsorbent, a material must have the capacity to take up at least 10 g or water per g of solids [1], and the system also should be resistant to squeezing [2]. Articles considered in this review chapter most often report absorption capacities in

the range 100–1000 g water per g of superabsorbent polymer. It has been shown that certain chemical derivatives of cellulose, in particular carboxymethylcellulose (CMC), can indeed be used as a main ingredient of superabsorbent hydrogels [3]. Cellulose itself – in the form of fibers, nanofibrillated cellulose (NFC) and cellulose nanocrystals (CNCs) – can potentially be employed as components in highly absorbent hydrogel systems. So, in considering the mechanistic role of "cellulose," the present chapter takes a broad view, considering everything from native lignocellulosic fibers, to nanocellulose products, to water-soluble polymeric derivatives of cellulose for use in highly absorbent products. The fact that cellulose can fulfil so many different and overlapping roles in absorbent-related technologies attests to the unique nature of this remarkable macromolecule. The wider topic of superabsorbency also has been addressed in earlier review articles [1, 2, 4, 5].

Daunting challenges need to be overcome if the goal is to replace the currently used superabsorbent products with cellulose-based materials. Over 90% of the superabsorbent polymer (SAP) presently in use is based on acrylic-based polymers, i.e., lightly cross-linked sodium polyacrylate hydrogels. This is the major absorbent material in disposable diapers and feminine pads. Because manufacturing costs for such SAPs are presently much lower in comparison to any natural-based superabsorbent materials, it is reasonable to expect that the acrylate-type SAPs will remain dominant in the market for the foreseeable future. On the other hand, polyacrylates are derived from petroleum resources, which eventually will become depleted. Though the transition from a fossil resource-based economy to a sustainable economy has been slow, it is important to pursue steps in that direction. One of the most important contributions that researchers can make toward more rapid implementation of cellulosic materials in disposable absorbent products is to find ways to lower the costs of manufacturing such products as CMC.

2 Why Cellulose

2.1 General Aspects

Cellulose is highly available, relatively low in cost, and, at least in its native state, highly eco-friendly. The amount of cellulose grown annually on the planet through photosynthesis has been estimated to be in the neighborhood of 10^{17} g [6]. Though much of the total cellulose that grows each year either decays, is burned for fuel, or is used for wood products, the amounts converted into papermaking fibers, chemical-grade cellulose (dissolving pulp), grown as cotton, etc. are still very large. Table 1 provides some estimates of the amounts of cellulose, in various forms, that are produced in the world each year. Note that the amount of "fluff pulp" shown in the table is highly relevant to the focus of this chapter, since fluff pulp is a major component of typical disposable diapers and other highly absorbent products [7, 8].

Another main component of typical disposable diapers, incontinence pads, tampons, and other such product is superabsorbent polymer (SAP) hydrogels. These currently are mainly based on poly(acrylic acid) or copolymers of acrylic acid and

Table 1 Estimates of annual world production of various classes of cellulose vs. superabsorbent polymer market

Category of cellulose	Annual production (g)	Citation
Total cellulose growth	10^{17}	[6]
Total nontropical forest cellulose growth	3×10^{15}	[6]
Harvested wood (assuming 1 $m^3 = 10^6$ g)	10^{15}	[9]
Delignified fiber (kraft pulp, etc.) production	10^{14}	[10]
Kraft fluff pulp for absorbent products	7×10^{12}	[11]
Dissolving-grade pulp production	2.6×10^{12}	[10]
Current superabsorbent polymer production	2×10^{12}	[12]
Current carboxymethylcellulose production	5.4×10^{11}	[13]

acrylamide, which are nonrenewable, petroleum-based products [8, 14]. A hydrogel will be defined here as a hydrophilic polyelectrolyte having a range of cross-linking that allows it to swell in water but not dissolve. The amount of synthetic SAPs used per year is over 1.5×10^{12} g [5, 12]. By comparing this number with other data shown in Table 1, two things become clear. First, the amount of SAP being produced each year is just a tiny fraction of the amount of cellulose that is being isolated each year in various forms. Second, the amount of SAP is larger than the current worldwide production of carboxymethylcellulose, and it is almost of the same magnitude as the world production of dissolving pulp, which has a variety of current uses. It follows that, if it were decided to replace the present SAP output with cellulose products, the present production capacity for dissolving-grade pulps would not be sufficient.

Perhaps to a greater extent than its abundance, one of the primary reasons that researchers have been motivated to consider cellulose as a source for making highly absorbent products is the environmentally friendly nature of the raw material. Since cellulose is produced naturally by photosynthesis, its usage in place of petroleum-based chemicals has the potential to reduce the net production of carbon dioxide [15]. Based on the assumption that the forests from which wood is obtained are replanted and managed in an efficient and sustainable manner, such practices have the potential to minimize the production of greenhouse gases over the long term.

Although biodegradability has been viewed as an inherent advantage of cellulose-based products, compared to petroleum-derived SAP, a critical examination is needed of each case. On the one hand, native sources of cellulose (e.g., wood, cotton, bacterial cellulose, etc.) all are subject to natural decay [16, 17]. Researchers have shown that various cellulose-based sorbent materials are biodegradable [18–27]. Acrylamide-based or acrylic acid-based materials generally exhibit slow degradation rates [28–31]. However, under well-managed composting conditions, favorable rates of decomposition acrylic acid-based disposable diapers, including detoxification, have been reported [32, 33].

Rates of biodegradation of polymers, including natural polymers, will be affected by chemical modifications. For instance, carboxymethylcellulose is readily degraded

by cellulase enzymes [34]. But other chemical transformations, such as chemical derivatization and cross-linking (see later sections), sometimes have a negative effect on biodegradation [35]. A further difficulty is that SAP-containing products are often buried under conditions where any degradation is either very slow due to lack of oxygen or where decomposition results in the production of methane, which is a highly potent contributor to global warming [16, 17, 28]. There is a continuing need for environmental impact assessments to compare petroleum-based superabsorbent products and similar products based on CMC or other natural-based materials [36, 37]. Future studies will be needed in order to confirm the working hypothesis here that (a) cellulose-based absorbent products are likely to be more biodegradable than currently used SAP materials and (b) the greater biodegradability can have an important ecological advantage either when using state-of-the-art waste disposal practices. Future alternative processes might be based on composting [32, 33, 38, 39] or anaerobic treatments with efficient retrieval of methane [40, 41]. Incineration is often regarded as unattractive due to the high water content of used SAPs [42].

2.2 Chemical Aspects

Two main aspects of cellulose that are likely to be important for the preparation of absorbent products will be considered in this section – the generally hydrophilic nature of cellulosic materials (with attention to the role of –OH groups) and the ionically charged nature of many cellulosic materials, with particular focus on $–COO^-$ groups.

As is well known, pure cellulose is a homopolymer of anhydroglucose units that are joined together by β-glycosidic bonds. Each six-carbon glucose unit contains three –OH groups. Native cellulose from wood commonly has degree of polymerization (DP) values in the range of about 3000–5000 [43]. In woody plant materials, cellulose is present in combination with hemicellulose and lignin, of which the hemicellulose generally causes the mixture to be more hydrophilic [44, 45] and the lignin causes the combined material to be more hydrophobic [46]. Cellulosic plant materials also contain relatively small amounts of extractives, most of which contribute to a hydrophobic tendency [47]. The percentages of these components, in typical wood from temperate climates, fall into ranges of about 40–45% cellulose, 25–35% hemicellulose, 20–30% lignin, and 2–5% extractives [48]. Cotton represents a special case of cellulosic material; as a seed hair material, it consists mainly of cellulose, but in nature it has a hydrophobic coating of wax [49].

Processing of cellulosic materials can change their chemical composition greatly. For example, the kraft pulping of wood and other materials such as sugarcane bagasse and bamboo is intended to remove mainly the lignin portion, along with most of the extractives and a portion of the hemicellulose [48, 50]. By contrast, mechanical pulping of wood typically achieves separation of the fibers from each other while maintaining a yield of over 90% of the original solids. Processing of cotton typically entails removal of the natural wax [49].

2.2.1 Hydrophilic –OH Groups

Due to its polar nature and its ability to participate in hydrogen bonding, the –OH group is well known to contribute to the water-loving nature of many organic compounds [51]. The greater electronegative character of the oxygen atom, compared to that of hydrogen, creates a dipole of approximately 1.7–2.5 D [52]. In aqueous solutions, such dipoles contribute to a transient (pico-second duration) lining up of –OH groups belonging to the water, as well as to other compounds [53], and the energy of such interactions contributes to wetting and solubilization of various materials in water. Due to its partly crystalline structure (see later), the cellulose does not dissolve, though it is generally agreed that the polar interactions are favorable for the swelling of cellulosic materials in water [54].

A second way that –OH groups can contribute to hydrophilic character is via hydrogen bonding. The hydrogen atom is unique in nature in having only one electron per atom. When a hydrogen atom is covalently bonded to oxygen, a more electronegative atom, the pair of electrons participating in bonding (or the density of the wave function) tends to spend a disproportionate amount of time or be enriched near to the oxygen [55]. This leaves the hydrogen nucleus (a proton) relatively exposed and available for secondary interactions with the lone pairs of electrons on the oxygen atoms of other water molecules in the neighborhood. The hydrogen bonds thus formed have energies ranging from about 1.4 to 7 kcal/mole [56]. The lifetime of an individual hydrogen bond in the bulk phase of water is about 0.4×10^{-12} s [57]. The ability of hydrogen bonds to very rapidly form and detach from each other, in a continually shifting structure, helps to account for the strong cohesive forces within water, in combination with an ability to flow as a liquid, if not frozen. Figure 1 provides a pictorial representation of an –OH group-rich cellulosic surface with a "snapshot" of possible orientations of water molecules as they participate in transient preferential orientations with the surface groups and as clusters with each other [53].

Though there are three –OH groups for each anhydroglucose unit that comprises cellulose, only a small portion of such groups are typically available for interaction with the surroundings, including water molecules. That is because a large proportion of such groups will be arranged in highly organized patterns of intramolecular and intermolecular hydrogen bonding within the cellulose phase [58]. Typical native

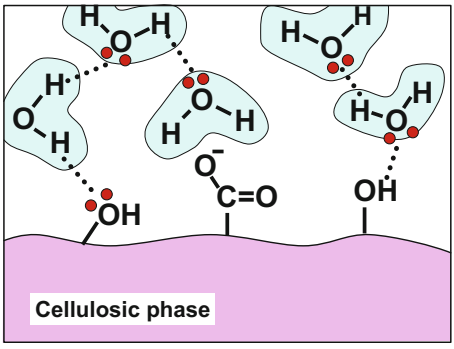

Fig. 1 Schematic diagram illustrating a possible transient orientation of water molecules at a cellulosic surface under the influence of polar interactions and hydrogen bonding

celluloses have crystalline contents in a range of about 40–80% [59], and it is clear that –OH groups located in the interior of such regions have essentially no ability to participate in interactions with water molecules [60].

2.2.2 Charged $–COO^-$ Groups

Native cellulose, in its raw forms, is of neutral charge in aqueous suspension. However, ionic functional groups attached to cellulose chains can play a large role in the ability of cellulosic materials to swell in water. To begin with, hemicellulose macromolecules of various types either already contain carboxylic acid functionalities or they contain acetate groups that can be easily converted to charged form by hydrolysis reactions [61]. Further amounts of $–COO^-$ groups are provided by lignin structures [48] and by various extractives, such as fatty acids and resin acids [47, 48]. Table 2 provides some typical values for the amounts of $–COO^-$ groups within native woods, compared to those in a cellulose derivative and polyacrylate.

The energy associated with the interaction of a $–COO^-$ group (in its Na^+ salt form) with surrounding polar water molecules is approximately 4 kcal/mole [65]. This value may at first suggest that ionic groups will have a large influence on swelling and absorbency properties of cellulosic materials. But that will be true only when the densities of such groups are either naturally high (e.g., due to the presence of hemicellulose) or that there has been chemical derivatization of the cellulosic material. Common cellulosic fiber materials have carboxylic acid contents ranging from just 5 μeq/g in the case of cotton to about 44–66 in the case of bleached hardwood kraft pulps [62]. These are very low values in comparison to SAPs, as shown in Table 2. Thus, for purposes of achieving high absorbency of water, there is a strong motivation to consider chemical derivatization as a means of increasing the charge density and increasing the absorption capacity of native cellulose.

Figure 2 depicts the main reaction for the preparation of carboxymethylcellulose (CMC), usually starting with dissolving pulp (e.g., highly delignified wood pulp) [66]. Commercial grades of CMC are widely available. The degree of substitution (per anhydroglucose unit) can range from about 0.4 to about 2.2 [18, 63, 64]. A DS value of 0.4 is generally high enough to allow solubilization of the polymeric material, as long as the pH is high enough to dissociate the carboxylic acid groups. But it is the relatively high-DS CMC products, with their correspondingly higher swelling tendency and strong solubility in water, which are regarded as promising components of highly absorbent hydrogels [18]. Such hydrogels are often cross-linked by application

Table 2 Typical levels of carboxylic acid groups in common cellulosic materials

Type of cellulosic material	Carboxylic acid content (μeq/g)	Citation
Cotton linters	5	[62]
Bleached softwood kraft fibers	29	[62]
Bleached hardwood kraft fibers	44–66	[62]
Unbleached softwood kraft fibers	83	[62]
Carboxymethylcellulose (DS 0.64–2.2)	3277–8127	[18, 63, 64]
Polyacrylic acid, sodium salt	10,600	Calculated

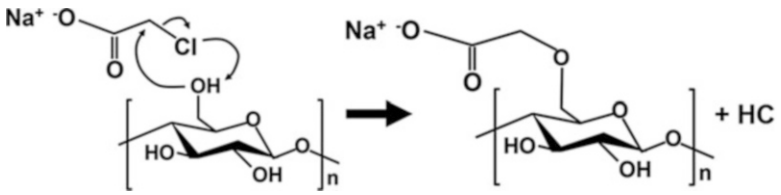

Fig. 2 Alkali-catalyzed reaction of cellulose with chloroacetic acid (sodium form) to produce carboxymethylcellulose (CMC)

of gamma radiation [16, 18, 19, 64, 67]. Though highly absorbent materials also can be obtained with other ethers and esters of cellulose, the results generally have not been as favorable as those achieved with CMC [68].

An alternative way to increase the level of carboxylic acid groups at the cellulose surface is by grafting. For example, Gurdag et al. [69] and Margutti et al. [70] carried out pioneering work in the grafting of acrylic acid chains to cellulose. The resulting structures from such reactions show greatly enhanced water-absorbing capabilities.

Another chemical reaction that has important implications for cellulose-based absorbent products is formation of sulfate ionic groups, which are often referred to as sulfate half-esters [71]. As will be described more in Sect. 2.3.4, treatment with concentrated sulfuric acid is widely used for the preparation of cellulose nanocrystals (CNCs). In addition to liberating the crystals, such treatment yields cellulosic surfaces that are covered with $–OSO_3^-$ ionic groups. Since sulfuric acid is a strong acid, such groups maintain their negative charge throughout the range of pH values considered by most investigators. Zhang et al. [72] showed that sulfate half-ester groups can be especially effective in increasing the water retention value [73] of bleached kraft fibers.

2.3 Structural Aspects

Absorbency typically involves swelling of an absorbent material, i.e., a change of it dimensions as the liquid enters. It follows that structural aspects of cellulosic materials, including their ability to expand or their tendency to restrain expansion, can affect absorption performance.

Some aspects of cellulose material structure are determined by its chemical composition, while others are related to details of plant growth. Yet others are related to the higher-level organization of cellulose, hemicellulose, and lignin into fibers and larger parts of woody plants. Further structural details depend on how the cellulosic material may have been separated into component fibers (i.e., pulping) or subsequently converted to nanofibrillated or nanocrystalline forms. These structures, if present, may affect properties of the absorbed products, so some aspects will be considered here.

2.3.1 Inherent Structural Tendencies of Cellulose

Cellulose is inherently fibrillar. This characteristic becomes clear if one attempts to prepare spherical cellulose structures at a nanoscale [74]. When cellulose is precipitated from solution, usually by introducing a non-solvent or otherwise changing the conditions of the medium, the precipitated matter is generally in the form of fibers or an extruded filament or sheet composed of fibrillar elements at the nanoscale [75]. This behavior can be attributed, at least in part, to details of cellulose's molecular structure – which is linear, free of branches, and having –OH groups in a suitable position to form both intra-chain and interchain hydrogen bonds [58]. The intramolecular bonds tend to hold the molecules in a straight-line position. The tendency for linear alignment is reinforced by the action of hydrogen bonding that can develop between adjacent cellulose molecules, especially if the chains are lined up in parallel. The molecular conformation, including the participation of hydrogen bonds in that conformation, has been confirmed by X-ray crystallography [58] as well as by molecular dynamics simulations [76].

During biosynthesis of cellulose, there is evidence that individual cellulose chains are formed from glucose in six-sided rosette-shaped proteinaceous structures in the cell walls of plants [77] and that the extruded chains somehow come together in a parallel, proto-crystalline form [78]. The result, in typical plant materials, is the formation of crystalline zones having widths of about 3–8 nm [79]. In woody plants, these crystalline zones are enmeshed within a matrix of noncrystalline components, mainly consisting of hemicellulose and lignin [48]. In addition, X-ray crystallography consistently indicates that some of the cellulose is also present in either a noncrystalline (amorphous) form or at least having defects in the pattern of crystallinity [79]. For instance, Nishiyama et al. [80] found evidence that sequences of approximately 4–5 anhydroglucose subunits tend to deviate from crystallinity within native cellulose material and that the adjacent parts of the chains are within crystalline zones. It is widely believed that these noncrystalline zones of cellulose have an enhanced tendency to interact with water [60, 81, 82].

At nano-dimensions, the ability of cellulosic materials to swell and accommodate water is generally attributed to either (a) swelling of noncrystalline zones or (b) opening up of spaces between crystalline zones, i.e., a form of partial nanoscale delamination.

2.3.2 Fibers

A typical softwood kraft fiber of the "fluff pulp" type [7] will readily take up about 12 g or water per g of solid matter [1, 5]. Though this value is high enough to meet Kabiri's [1] criterion of superabsorbency, as given earlier, it is well known that water can be easily squeezed from fluff pulp. To understand why fluff pulp takes up water so readily, it can be useful to consider the layered structure of natural fibers in wood, as illustrated in Fig. 3.

The mechanical ability of kraft fibers to increase their radial dimensions when exposed to aqueous solution can be understood based on the directionality of cellulose macromolecules and microfibrils within the dominant (S2) sublayer of the cell wall [83]. Within that layer, the chains are oriented not far from a parallel

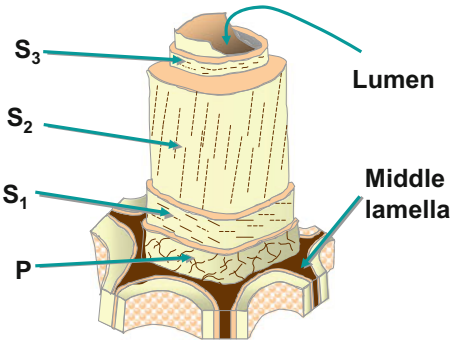

Fig. 3 Schematic diagram of a fiber within wood, showing the relative thicknesses of different layers and indicating the predominant orientation of cellulosic macromolecules and fibrils in those layers

alignment (often deviating by 10–15°) from the fiber axis. Since the stiffness and crystalline content of the fibrils prevents them from stretching much in the lengthwise direction, most expansion resulting from immersion in water occurs perpendicular to the fiber length. Within intact wood such swelling is limited by three factors, namely, (a) the presence of a stiff, relatively hydrophobic lignin-rich zone (the middle lamella) that joins the fibers to each other; (b) the presence of an S1 layer, in which the cellulose macromolecules and microfibrils essentially wrap around the fiber circumferences, thus constraining their outward expansion; and (c) the close integration of the cellulose microfibrils with densely packed matrix materials, mainly lignin and hemicellulose. Eriksson et al. [44] showed that selective removal of lignin from solid wood greatly increased the uptake of water. Chemical pulping, employing such reagents as NaOH and Na_2S, can effectively remove lignin and a part of the hemicellulose, thus rendering the material porous within a range of about 2–100 nm [84]. The mesoporous nature can be regarded as a first step in enabling subsequent internal delamination and swelling of the fibers.

Delamination and swelling of delignified fibers is further enabled if and when the fibers are subjected to mechanical refining, which is an almost universal practice when preparing the fibers for papermaking. Common refining practices entail passage of a 4–8% solid suspension of fibers between a rotor and stator having raised rectangular "bar" areas, which repeatedly compress and shear bunches of the fibers. Even a relatively short application of refining, especially after delignification, is able to break up and remove both the primary (P) layer and the S1 sublayer, such that the remaining material in the S2 layer is no longer impeded from expanding outward from the fiber axis. The shearing action of refining also tends to open up spaces between fibrils within the S2 layer, causing partial delamination. Concurrently, the fibers become increasingly swollen with water.

At this point in the discussion, a reality check may be helpful. Although an ordinary paper towel can take up about 5–10 times its mass of water [85], this is only a minor fraction of what is expected for modern superabsorbent materials, e.g., an absorbency mass ratio of 100–1000. While kraft fibers may constitute a major component of such products as disposable diapers, it is clear that they do not account for the majority of the absorbency. Fluff pulp fibers, which are about 3 mm long and about 30–50 μm thick, provide three main functions within highly absorbent

products: providing a place for the SAP to be contained, serving as channels for the wicking of liquid so that it can reach all the SAP quickly, and providing structure to the highly absorbent garment.

2.3.3 Nanofibrillated Cellulose (NFC)

Very extensive mechanical refining of cellulosic fibers, such as from kraft pulps, cotton, and other plant sources, will eventually yield a highly swollen, gelatinous mass that is mostly water but highly viscous [86, 87]. The solid material within such gelatinous mixtures is highly fibrillated cellulose, in which the individual strands may have diameters in the range of 20–60 nm [88]. Rather than consisting of individual fibrils, most published images of NFC (or microfibrillated cellulose, a term often used when the material has not yet been reduced to nano-dimensions), the material is usually described as a network, or "highly branched," or a "weblike structure" [88]. Although the term "cellulose nanofibrils" (CNF) is widely used in the literature for the products of such preparations, that term does not appear to be well suited to describing the highly branched and networked structures most often described in the studies that were considered when preparing this chapter. Equipment used for production of NFC includes not only conventional refiners, of the type used by papermakers, but also "micro-grinders," in which the pulp is passed multiple times through the gap between a rotor and stator with abrasive mineral surfaces [89]. Alternatively, as shown in Fig. 4a, NFC can be produced by multiple passes through a high-pressure homogenizer, where the suspended material is forced through a narrow gap, within which the solids impinge on a hard surface [90]. In another type of device, the microfluidizer, jets of cellulose suspension are made to impinge upon each other, bringing about mutual fibrillation with less wear of the equipment (Fig. 4b) [91]. In a patented approach, highly fibrillated cellulose also can be prepared by co-grinding in the presence of a suspension of calcium carbonate particles [92].

The production of NFC by mechanical action alone requires a high input of energy [88]. For instance, 70,000 kWh may be required to prepare NFC by homogenization [44]. Such a high consumption of energy is not only environmentally unfavorable, but it also tends to reduce the chance that NFC would be employed as a component in future highly absorbent products. To reduce the required energy, several approaches involving chemical treatments have been demonstrated. Selective oxidation with (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) has been shown to be particularly effective in promoting fibrillation of cellulose with much less energy. Such treatment was found to decrease the required mechanical energy to product NFC by as much as a factor of 100 [93]. The much reduced energy of processing of the oxidized pulp has been attributed to the ionic charges of the $–COO^-$ groups (especially at pH values above about 4), which promote swelling, fibrillation, and internal delamination. The water retention value of NFC, produced by such treatment, can be in the range 1700% [94]. The oxidation reaction is diagrammed in Fig. 5. As shown, the TEMPO-mediated oxidation selectively forms carboxylic acid groups at the C6 position, while having only a minor effect on the anhydroglucose rings of the macromolecule [93]. Similar effects have been

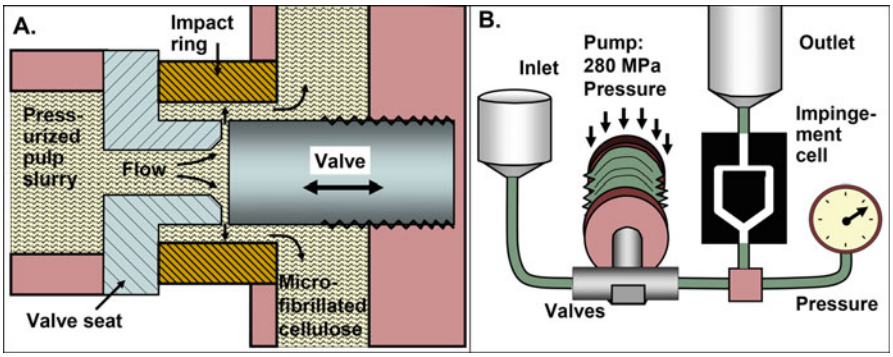

Fig. 4 Two devices for production of nanofibrillated cellulose (**a**) high-pressure homogenizer; (**b**) microfluidizer

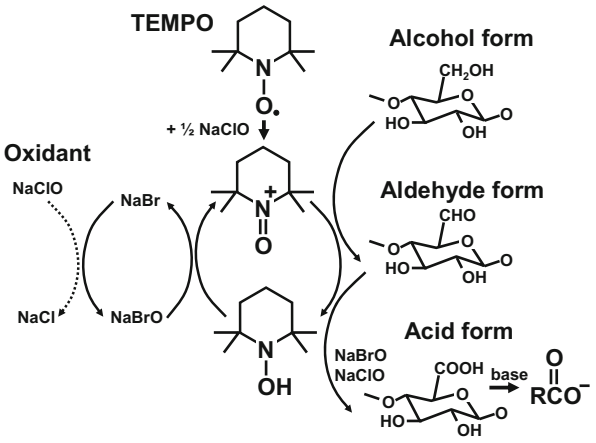

Fig. 5 Reaction scheme for TEMPO-mediated oxidation of a cellulosic material

achieved by treatments with periodate/chlorite oxidation [95, 96] and by carboxymethylation [97].

Another promising approach consists of an optimized treatment with cellulase enzyme [98]. Such treatments must be performed with careful attention to concentrations, temperatures, treatment times, etc., since the enzymes preferentially attack noncrystalline and nanoscale fibrillar parts of the cellulose. Thus, excessive treatment can be expected to break down and solubilize the class of material that one is attempting to form. Pääkkö et al. [98] showed that the optimized use of cellulase, in combination of mechanical energy, can make it possible to produce NFC with less energy consumed.

2.3.4 Cellulose Nanocrystals (CNCs)

Digestion of cellulosic material in strong acid, under optimized conditions, gives rise to cellulose nanocrystals, which also can be considered as a component in certain

highly absorbent materials. The technology of producing CNC has been reviewed [99, 100]. Briefly stated, the strong acid treatment preferentially hydrolyzes the noncrystalline or defect areas in the material, leaving behind crystals having thickness dimensions in the size range of about 4–70 nm [99, 101]. Though the acid eventually would also hydrolyze the crystals, the rate of hydrolysis is sufficiently slower so that it is possible to isolate suspensions of highly uniform crystals. Cheng et al. [102] reported a water retention value of 3.4–3.5 g/g for a water suspension of CNC.

The lengths of CNCs vary widely, depending on both the source material employed and the conditions of preparation [99, 101]. It is possible to shorten the crystals after their preparation by crushing them in the presence of liquid nitrogen [103]. The longest CNC particles, up to several micrometers, have been reported for tunicate cellulose, obtained from the protective spines of marine animals [99, 101]. Lengths of CNCs obtained from wood (after delignification) are typically in the range 100–250 nm [99].

3 Absorbency Mechanisms

The uptake of aqueous solution by cellulose-based products is affected by the chemical groups and structural factors discussed in the previous two sections. As has been described in more detail elsewhere [5, 104–110], one can envision there being competition between certain chemical factors tending to solubilize and swell the material and various structural contributions that prevent complete dissolution and may limit the amount of swelling in a specific case. The chemical factors will be considered here first.

3.1 Hydrophilicity

As was mentioned in Sect. 2.2.1, the formation of a hydrogen bond between a water molecule and an available –OH group on a cellulosic surface releases approximately 5 kcal/mole of energy. This implies that the wetting of dry cellulosic material is favored by the ability to form such bonds with water. One of the greatest uncertainties, when trying to estimate the relative importance of hydrogen bond formation as a contributor to the uptake of water by cellulosic materials, is the fact that only a fraction of the –OH groups on cellulose chains may be available to participate in such interactions. In such materials as wood and cotton, roughly 70% of the cellulose may be in crystalline form, and it has been shown that crystalline regions are essentially impenetrable to water molecules [60]. On the other hand, typical plant-derived cellulose is likely to contain hemicellulose (except in the case of certain dissolving pulps and cotton), and the hemicellulose remains amorphous and much more able to interact with water molecules. A search of the literature did not indicate any work to estimate the density of water-to-cellulose hydrogen bonds formed upon the immersion of common cellulosic materials. Thus, this would appear to be an

excellent area to proposed future research. In particular, it is reasonable to expect that measures to reduce the crystallinity of cellulose, e.g., by chemical derivatization or ball milling [111], would be expected to increase the amount of water-to-cellulose hydrogen bonds in a given mass of material.

The interaction of a water molecule with an ideal cellulosic surface, creating a monolayer coverage, will be energetically favored by hydrogen bonding, but what about subsequent layers of water? Studies of the energetics of water sorption, at a molecular level, indicate that the adsorption of a first and possibly a second layer of water can involve different amounts of energy, compared to the energy of water association with itself in the bulk of solution [112]. However, such differences tend to become unimportant after about five molecular layers of water [113]. This is a key point if one's goal is to achieve superabsorbency. Even if the cellulose-based material has been transformed in a way to make every –OH group available for interaction with water (essentially solubilizing the material), the hydrogen bonds subsequently formed with one, two, or even three layers of water molecules surrounding each cellulosic –OH group (including those from hemicellulose, if present) might not be enough to achieve superabsorbent behavior.

3.2 Dissociation

Another large contribution to the energy of interaction between water molecules and a cellulosic surface can come from ionized groups. As noted in Sect. 2.2.2, the energy of solvation of an individual ionic group in water is about 4 kcal/mole. Whether this is enough to make an important contribution depends not only on how many such groups are present, but also on whether or not the groups are in their charged form. As mentioned earlier, although native cellulose is essentially uncharged, there can be up to about 1000–3000 μeq of carboxylic acid groups per gram the hemicellulose component in typical papermaking pulps [114]. This amount will depend on the type of hemicellulose and whether or not acetyl groups have been hydrolyzed during processing to convert them to –COOH or $–COO^-$ groups [61]. Salam et al. [115] showed that increased absorbency can be achieved by incorporating additional carboxylate groups into hemicellulose.

Carboxylic acid groups can undergo dissociation reactions of the type shown in Eq. 1. In its protonated form, though the carboxylic acid group is capable of participating in hydrogen bond formation [116], it is uncharged. Reaction with one mole of alkali converts the group to its charged, carboxylate form. In the discussion that immediately follows, it will be tentatively assumed that sufficient base is present that the groups are at least mostly in their charged form.

$$RCOOH + NaOH \rightarrow RCOO^- + Na^+ + H_2O \quad (1)$$

In order for there to be a sufficient density of ionic groups to meet the requirements of superabsorbent materials, the carboxylic acid content has to be much higher than what is found in natural cellulosic materials. Most research for the

development of highly absorbent cellulose-based materials have been based on carboxymethylation [3]. Superabsorbent materials with water uptake ratios in the range 20–800 have been achieved with the use of carboxymethylcellulose (CMC) [18, 19, 63, 64, 67, 68]. Even higher levels of water uptake have been achieved with copolymers of CMC and acrylic acid or related monomers [25, 117–129]. In such cases, the level of carboxymethylation is typically in the range of 0.64–2.2 substitutions per anhydroglucose unit. Water absorption capacities in the range 40–1400 g/g have been reported with SAPs based on ordinary CMC.

3.3 Osmotic Pressure

Bound ionic charges within a polymeric material, when it is placed in pure water, create an imbalance of ionic charges vs. location. Because the bound charges cannot move away from the polymer segments, the counterions to the bound groups will be constrained to remain nearby, and there will be a higher concentration of ions in the neighborhood of the polymer segments compared to the bulk of solution. To rectify the imbalance, water molecules will spontaneously diffuse into the charged polymeric material, swelling it, thus increasing the average distance between adjacent charges. Since the range of electrostatic effects can extend to several nanometers, especially in relatively pure water, such effects can involve high ratios of water mass to solid mass, leading to high swelling ratios. Related theories have been applied to hydrogels, including cellulose-based materials [104, 109, 130–134].

The contribution of charged groups to the swelling of a charged polymeric material in water can be expressed in terms of an osmotic pressure, as given by Eq. 2 [109].

$$\pi = RT\left[\Phi\sum_i \overline{C_i} - \phi\sum_i C_i\right] \tag{2}$$

In the equation, Φ is the osmotic coefficient of the external solution, and ϕ is the corresponding quantity for the gel phase. Likewise, $\overline{C_i}$ is the concentration of the ith species in the gel phase, and C_i is the corresponding value in the bulk phase. In principle, the material will continue to expand until there is a balance between the osmotic pressure and a restraining pressure, which may be related to the strength of the material or the manner in which it may be attached together. For example, cross-linking of the macromolecular material may limit its ability to stretch past a certain extent. Alternatively, one might model the solid material in terms of mechanical springs, which represent the resistance to swelling. Scallan and Tigerström [135] showed that such reasoning can be used to estimate the elastic modulus of absorbent cellulosic material in its water-swollen state. Other contributions to net swelling of a hydrogel are contributed by the entropy of mixing and hydrogen-bonding effects [3].

4 Factors Affecting Swelling Extent

The extent of swelling and absorption capacity of cellulose-based materials, including cellulosic fibers and various kinds of hydrogels, depends on many factors, some of which involve the nature of the absorbent materials, and others that depend mainly on what is in the aqueous environment. It will be assumed here, for the sake of discussion, that some form of cross-linking usually will provide the main resistance to swelling. As pointed out by Scallan [104], similar reasoning can be applied to other situations, such as when diffusion of a charged polymeric material is constrained by a semipermeable membrane.

4.1 Cross-Link Density

As outlined in an earlier review [3], several different kinds of cross-linking agent have been employed in published studies of cellulose-based hydrogel materials. Typically, when considering cross-links, one is interested in compounds capable of forming pairs of covalent bonds, thus connecting polymeric segments to each other. In addition, it is important to also consider the role of nanocellulose, which has been shown in some studies to produce effects that have similarities to those of cross-linking agents.

4.1.1 Conventional Links

As illustrated in Fig. 6, with increasing density of cross-linking among the polymeric chains of the material, there is less and less distance that the adjacent chains can move away from each other, on average, before they reach their limit. Studies of cellulose-based hydrogels generally have shown strong correlations between cross-link density and absorption capacity [18, 19, 26, 64, 136, 137]. The highest absorption capacities reported tend to be observed at the lowest cross-link densities considered [19]. One needs to be cautious, however, since the lower limit of practical cross-link density may be governed by how much cross-linking is needed to avoid

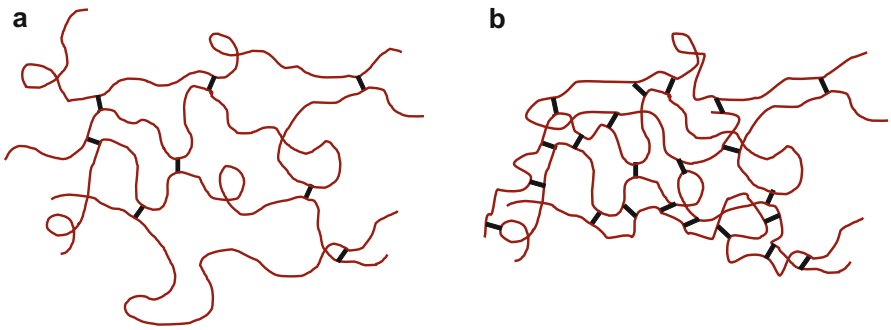

Fig. 6 Schematic illustration of the effects of cross-link density on the swelling ability of hydrophilic polyelectrolyte chains (**a**) low density; (**b**) higher density or cross-linking

mechanical failure or outright dissolution of the gel material [138]. At the limit of low cross-linking density, the molecular mass of the charged polymer needs to be high, thus ensuring that most of the chains are bound by at least one covalent link to the rest of the material. A higher molecular mass has been shown to lead to higher absorption capacity of cross-linked CMC hydrogels [26].

4.1.2 Cellulose-Based Links

Some studies have shown that inclusion of nanocellulose within hydrogel formulations tends to reduce the uptake of water [2, 139–143]. In such cases, the role of the cellulosic material appears to be similar, in some respects, to that of cross-linking agents. Since no covalent bonding is suspected in most such cases, other explanations must be considered. One such possibility is to regard the nanocellulose as a reinforcement within a kind of composite, where superabsorbent polymer may play the role of matrix. There are many examples in which the presence of fibrillar nanocellulose tends to increase the modulus of elasticity of the continuous phase in cellulosic nanocomposite systems [144]. It also has been proposed that the presence of ordinary cellulose fibers within conventional disposable diapers and related products will tend to limit the swelling due to the fibers' resistance to tensile expansion [134]. The high aspect ratios of a cellulose nanofibril, as long as it is intimately associated with the swellable material, are assumed to be important relative to the restraint of swelling.

4.2 Aqueous Conditions

Water can be regarded as a uniquely effective medium for absorbing into and swelling up materials that are inherently hydrophilic and subject to the development of bound ionic charges, i.e., the kinds of highly absorbent materials being considered here. One reason why water is such a welcome guest within hydrogel materials is that it has a high dielectric constant, ε, thus making it an excellent solvent and stabilizer for ionic materials. But changes in the ionic composition of aqueous solutions can have very large effects on uptake by cellulose-based hydrogels and other absorbent materials. Three key factors to be considered in this section are pH, salt concentration, and the presence of multivalent cations.

4.2.1 pH

The proportion of charged carboxylic acid groups on cellulosic materials of various kinds is known to be a strong function of pH. The same principles apply to kraft fibers, CMC, and even to poly(acrylic acid). Kraft fibers, especially if they are rich in carboxylic acid groups, exhibit increased swelling as the pH is raised from acidic to neutral values [145, 146]. A similar trend, but with much higher levels of swelling, has been reported for CMC and for copolymers of CMC and acrylic acid [30, 63, 125, 126, 129, 147, 148].

Effects of pH can be understood based on Eq. 1, which can be rearranged as shown in Eq. 3 to define the acid dissociation constant K_a.

$$K_a = \left(\frac{[A^-][H^+]}{[HA]} \right) \tag{3}$$

The pK_a value can be defined by taking the logarithms of the terms in Eq. 3, where $[A^-]$ is the concentration of the conjugate base, $[H^+]$ is the concentration of the hydronium ion, and [HA] is the concentration of the associated form of the carboxylic acid.

$$pK_a = -\log_{10}(K_a) = \quad -\log_{10} \frac{[A^-][H^+]}{[HA]} \tag{4}$$

In general, there will be an equal number of charged and uncharged carboxyl groups when the pH is equal to the pK_a value, which is approximately 4.4 in the case of CMC [149].

Based on Eq. 4, one might predict that the relative amount of dissociated $–COO^-$ groups ought to increase from 1% to 99% within the pH range of one less than pK_a to one more than pK_a. That would be true if all of the carboxyl groups were equal and noninteracting. But the dissociation of one carboxyl group on a polyelectrolyte chain changes the electrical field in that part of the molecule and tends to discourage the subsequent dissociation of neighboring carboxyl groups [150]. The situation is analogous to the dissociation of citric acid, a compound with three carboxylic acid groups, along with three values of pK_a corresponding to the first, second, and third dissociation. The consequence, in the case of a relatively high-charge-density polycarboxylic acid compound such as CMC or polyacrylic acid, is that the charge-pH curve will tend to be spread out over a wider pH range compared to what would be expected for a simple monomeric compound such as acetic acid. On the other hand, once the pH is as high as 7 or higher, most of the carboxyl groups will be in their charged form.

Investigators sometimes claim that their hydrogels are “smart” due to their ability to respond to pH [151]. For instance, hydrogels that contain carboxylic acid groups tend to remain unswollen in the stomach, which is a highly acidic environment, but they become highly swollen (perhaps releasing a medical agent) in the alkaline environment of the intestine [152–155]. Such behavior is consistent with the dissociation of carboxyl groups when the pH is raised.

4.2.2 Salts

The presence of simple salts such as NaCl tends to limit the range over which electrostatic forces are able to act within aqueous media. The effect can be expressed as Eq. 5, where z_i is the valence of ions opposite to that of the charged body of interest, n_i is the concentration of that ion, e is the electron charge, ε is the dielectric constant of water, k is the Boltzmann constant, and T is the absolute temperature [156].

$$\kappa^{-1} = \left[\Sigma_i \left({z_i}^2 n_i \right) 4\pi e^2 / (\varepsilon kT) \right]^{-0.5} \tag{5}$$

The quantity κ^{-1} is proportional to the distance over which electrostatic forces maintain a given level of influence. It follows from Eq. 5 that osmotic effects, especially those that involve high ratios of water uptake to the mass of absorbent materials, ought to be diminished by the presence of increasing concentrations of salt. Indeed, there is ample evidence of the ability of salts to repress swelling, including such evidence in the case of cellulose-based superabsorbent hydrogels [128, 129, 157]. Many researchers are especially interested in comparing pure water to physiological saline, which is intended to represent typical electrolyte concentrations in human bodily fluids, e.g., the liquid within cells. In that case, various studies have observed an approximately 50% reduction in the amount of water taken up by CMC-based hydrogels with the addition of that amount of salts [3].

4.2.3 Complexation

A much greater repression of swelling can be expected if the aqueous solution contains multivalent cations [25, 125, 131, 151, 159–161]. The term "complexation" is often used when describing such interactions due to the fact that two or more carboxylate functions within the absorbent material may approach one multivalent positive ion simultaneously, thus forming a reversible bridge. Even in the case of divalent ions, such as Ca^{2+}, the effect can be strong enough to be able to prepare strongly bonded "wet wipes," which can be redispersed as fibers only when they become highly diluted with water of much lower Ca^{2+} content when they are flushed [162]. Even stronger deswelling effects have been reported when adding water-soluble aluminum products [151, 158]. Coagulant mixtures based on aluminum are known to contain ions such as Al^{3+} and $[Al_{12}(OH)_{24}AlO_4(H_2O)_{12}]^{7+}$ [163, 164]. The bottom line is that multivalent positive ion concentrations ought to be low when the goal is to achieve high levels of water uptake.

4.3 Temperature

The temperature can have various effects on water uptake capacities, and in some cases the effects can be dramatic. For instance, hydrogels prepared with poly-(*N*-isopropylacrylamide) (iPAM) have been reported to abruptly lose 80–90% of their capacity to absorb water when heated over a range of about 20 °C [165, 166]. Such effects have been attributed to changes in the elastic properties of the hydrogels [167]. In the case of typical CMC-based hydrogels, moderate increases in sorption capacity with temperature have been observed [64].

5 Factors Affecting Rates of Uptake

In many applications of superabsorbent hydrogels, one needs to be concerned not only with the amount of water taken up but also the rate of sorption. The topic of absorption rates by highly absorbent materials has been considered by others [110, 129, 168]. Although ordinary SAP materials can have very high capacity to take up

water, they sometimes can be very effective for blocking the flow of water. For instance, if a disposable diaper gets flushed by mistake, it can easily swell up and obstruct a drain pipe. Once a mass of SAP has become swollen with water, it has been observed that flow from one side to the other, even when encouraged by pressure, can essentially stop [106]. As implied by the word "gel," the material behaves as an elastic material, despite its high content of water. Flow through a compressed, water-swollen mass of SAP can be very slow indeed, sometimes making it difficult for the contained liquid to migrate to parts of the products where dry SAP particles may still be present. So one of the big challenges faced by producers of highly absorbent items has been to allow flow to take place readily within a partly wetted mass of superabsorbent material. One solution to this problem is to create some kind of channels within the material.

5.1 Diffusion

Before considering the possible roles of cellulosic materials with respect to flow within a highly absorbent product, this section will consider factors affecting the diffusion of water through a hydrogel. In particular, engineers need to optimize the size and shapes of SAP phases so that water can diffuse all the way to the core within a practical length of time, depending on the application.

The characteristic time required for diffusion to occur over a distance L can be computed by the Stokes-Einstein version of the equation for diffusion [169].

$$\tau = L^2\, 6\pi\eta a/(k_B\, T) \tag{6}$$

In Eq. 6, τ is the characteristic time for diffusion to take place over a distance L, η is the viscosity of the medium, a is the radius of the diffusing object (modeled as a sphere), k_B is the Boltzmann constant, and T is the absolute temperature. Related calculations have been developed to deal with various geometries of interest, such as diffusion into either spherical or cylindrical SAP bodies [109]. Models are set up on the assumption that water needs to diffuse through a swollen layer in order to reach a core of still-dry SAP. In general, such analyses have emphasized that SAP phases ought to be relatively small and interspersed by zones in which bulk flow can take place. Such predictions are consistent with the work of Tanaka and Fillmore [170], who found that the time constant for swelling of poly(acrylic acid) gels was proportional to the square of the final radius of the SAP.

5.2 Channels

5.2.1 Cellulose-Enabled Channels

A primary role of softwood kraft fibers (fluff pulp) in typical highly absorbent products appears to be to provide wicking of liquids throughout the structure

[106]. The ability of cellulose fibers to facilitate the wicking of water can be appreciated if one looks with a microscope at highly wettable paper that has been printed with aqueous ink-jet ink. Letters printed on such paper will appear ragged, with "feathered" edges. It has been proposed that a related process occurs when fluff pulp fibers are included in a mixture of SAP particles [106]. In other words, the edges of the fibers are expected to provide relatively unobstructed passage of aqueous fluids so that all of the available SAP, as needed, can participate in the absorption. To enhance the effect, fibers can be designed with a lobe structure, which is claimed to provide especially efficient channeling of water. In summary, whereas before about 1960, cellulosic fibers served as the main absorbent material in diaper materials [8], now, in disposable absorbent products, one of their main roles appears to be to provide wicking.

5.2.2 Other Channels through Hydrogels

Progress also continues to be made with respect to the preparation of acrylic-based SAPs, and researchers have shown that the wicking role of fibers can be replaced by forming channels in a completely different way [171]. Instead of relying on fibers, the SAP itself is formulated with gas addition in a way that preserves a network of channels.

6 Strategies to Promote Absorbency

Increasing the accessibility and placement of functional groups onto cellulosic materials are both primary strategies that have been used to increase the water-sorptive capacity of cellulosic materials. Sometimes these two goals are connected. For instance, high levels of chemical derivatization of cellulose can be instrumental in bringing about solubilization of the macromolecular chain, thus exposing the material to water in a more intimate manner.

6.1 TEMPO-Mediated Oxidation

The option of TEMPO-mediated oxidation merits special mention, relative to water-sorptive properties, since it can be used in combination with mechanical processing to achieve not only a reduction in the need for mechanical energy but also a strong contribution to absorbency [172, 173]. For instance, Brodin et al. [173] showed that TEMPO-mediated oxidation of kraft pulp, as a pretreatment before freeze-drying, resulted in highly porous material having a sorption capacity of 21–65 g/g. Especially in cases where the goal is to achieve high levels of absorbency without reliance on complete solubilization of the cellulose, it has been shown that high levels of water uptake can be obtained by TEMPO-mediated oxidation of nanofibrillated cellulose, followed by freeze-drying [98, 174–176].

6.2 Specialized Drying

Once cellulose has been processed to achieve high levels of fibrillation and water retention ability, it often would make sense to be able to store and ship such material in dry form. Unfortunately, such drying ordinarily will tend to irreversibly decrease the water swellability of the material, when it is subsequently placed in water [84, 146, 177]. An irreversible reduction in the ability of the cellulosic material to take up water again, after it has been dried, has been attributed to strong capillary forces, causing the material to be drawn together to molecular distances; at that point a highly regular pattern of hydrogen bonding can take place between the cellulosic surface [178]. To some degree, such effects can be overcome if there is a sufficiently high density of carboxylate groups, in their dissociated form [146]. For example, Butchosa and Zhou [179] showed that treatment of NFC with CMC could help preserve the ability of the nanocellulose to act as a thickener, even after it had been dried. Other promising strategies include the addition of salt before drying [180], though such a strategy can have disadvantages in various potential applications.

Promising results have been achieved in the preparation of highly absorbent aerogels from nanocellulose [181, 182]. Some such compositions have exhibited superabsorbent characteristics [183, 184]. One of the advantages of such materials is that, in principle, one can achieve high absorbency with products that consist mainly of air and cellulose, such that many potential uses can be considered, including food and medical applications.

7 Conclusion

In view of the publications considered in this review chapter, much progress appears to have been made in the development of highly absorbent materials based on carboxymethylcellulose and other forms of cellulose. Ordinary cellulosic fluff pulp fibers, as well as various kinds of nanocellulose, can be used to adjust the properties of such absorbent materials. Factors affecting absorption capacities, as well as rates of wicking, appear to be in line with what is known about the individual components, as well as concepts of absorbency.

8 Future Scope

The subject of cost will be an important area of focus for future research related to cellulose-based highly absorbent products. Because various aspects of cellulose-based superabsorbents have been well demonstrated [3], the fact that such materials have not yet gained an appreciable market share suggests that costs must be unfavorable relative to acrylic-based SAPs. It may be useful in future studies also to consider costs that presently are not fairly distributed in the economy. Such a study could investigate how the relative costs would change if each producer of disposable materials had to arrange for or to directly pay the costs of disposal. Such a study

could estimate the impact on costs if bio-based, sustainable technologies were given favorable economic treatment, for instance, through tax policies. Though many readers of this chapter are likely to be more interested in questions concerning chemistry, it will be important to collaborate with researchers attuned to issues of economics, logistics, and ethical issues related to highly absorbent products.

There appears to be a critical need for fresh thinking and research concerning the best way to dispose of used items containing superabsorbent materials. It has been widely assumed, in published articles, that the cellulose-based products, being inherently biodegradable, are therefore ecologically preferable to petroleum-based SAPs and related absorbent products. But the use of disposable diapers, in particular, places challenges on the already heavily burdened system for solids waste collection and disposal. Studies have shown that even quite highly "biodegradable" materials can take a long time to degrade under typical landfilling conditions [185, 186]. When degradation does eventually occur, usually under anaerobic conditions, one has to worry about the efficiency with which the released methane is collected [187]. The ecological implications of such a system needs to be compared against state-of-the art wastewater treatment systems [188], as well as options such as composting [32, 33, 39]. A well-planned and regulated program of manufacture, collection after use, and composting of highly absorbent products made with 100% compostable components appears to be an attractive option that merits further research attention.

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Novel Superabsorbent Cellulose-Based Hydrogels: Present Status, Synthesis, Characterization, and Application Prospects

6

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Abstract

Over the past century, hydrogels have emerged as an effective material for an immense variety of applications. This contribution provides a brief overview of recent progress in cellulose-based superabsorbent hydrogels, fabrication approaches, materials, and promising applications. Firstly, hydrogels fabricated directly from various polymerization processes are presented. Secondly, we review on the stimuli-responsive hydrogels such as the role of temperature, electric potential, pH, and ionic strength to control the role of hydrogel in different applications. Also, the synthesis route and its formation mechanism for the production of smart superabsorbent, macro- and nano-hydrogels are addressed. In addition, several applications and future research in cellulose-based superabsorbent hydrogels are also discussed in this chapter.

Keywords

Hydrogel · Polymerization reaction · Superabsorbent · Stimuli-responsive · Biopolymer

1 Introduction

Hydrogels are known as the water-absorbing polymeric materials that are able to form a flexible three-dimensional structure with about 90% of water in the gel base and 10% of polymer chains. The presence of cross-linking interaction between water and hydrophilic characteristic of polymer chains facilitates the water-insoluble product with significant mechanical strength and physical integrity [1, 2]. Since hydrogels can absorb up to 1000 times of dry weight in water, thus this water-absorbing polymers are favorable for a variety of applications, especially for human usage. There is rising demand for hydrogels to be used for personal care and hygiene (baby diapers, sanitary pads, adult incontinence pads, and soft contact lenses), pharmaceuticals (drug carrier system), food (gelatin dessert), agriculture (plant water crystals), and health-care products (scaffolds in tissue engineering, wound care dressings) [3]. In addition to the existing market demand toward the hydrogel, continuous R&D activities have created a new opportunity in the development of intelligent materials for the biomedical areas, such as therapeutics, sensors, microfluidic systems, nanoreactors, and interactive surfaces [4].

Among the various types of biomaterials (e.g., polymers, composites, ceramics, and metals), hydrogels have shown high biocompatibility, tunable biodegradability, improved water retention ability, controlled release (especially for medicine or nutrients), preservation of stored components, easy to modify due to the presence of polar hydrophilic surface, and so on [5]. However, the feasibility of applying hydrogels is still limited due to poor mechanical strength and the fragile nature of hydrogel. In addition, majority of the hydrogels are produced from synthetic polymers (e.g., polyethylene glycol, polyamides, poly(acrylic acid), poly (methacrylamide), poly(*N*-isopropylacrylamide), poly(hydroxyethyl methacrylate)), which is limited particularly in the food industry, due to the likelihood of impurities

in the final product that may cause toxicity and potential environmental hazards [6, 7]. Therefore, novel or natural hydrogels with improved characteristics are still needed and will continue to remain an important direction for research.

Natural hydrogels are mainly derived from natural resources, such as alginate, chitosan, carrageenan, collagen, protein/peptides, matrigel, fibrin, gelatin, hyaluronic acid, and cellulose fibers. These materials render long service life, high capacity of water absorption, biodegradable, high biocompatibility, and high gel strength, which are the green alternative for synthetic polymers [8]. Cellulose fibers are nontoxic and low-cost organic polymers in the form of polysaccharide, which consists of hundreds to thousands of glucose units $(C_6H_{10}O_5)_n$. It is an abundant lignocellulosic biomass which is found mostly in forestry wood, agricultural residues, industrial wastes, and municipal solid waste [9]. Cellulose consisted of active hydroxyl functional groups (–OH), which can easily develop desirable hydrogels with tailored properties and product structure by chemically modifying the functional groups or using various types of synthesis technologies. Thus, the utilization of green cellulose materials for hydrogels can overcome the limitation of synthetic hydrogels, with enhanced properties that satisfy the requirement particularly in food and biomedical industry [10].

In this chapter, different hydrogel preparation technologies for synthetic and natural hydrogels will be discussed. In addition, focus toward the cellulose-based superabsorbent hydrogel was highlighted with a closer discussion on different kinds of stimuli-responsive cellulose-based hydrogels. The relationship between cellulose structure with hydrogel characteristics (mechanical strength, viscoelasticity, stress-strain, and swelling ability) was covered in this study. Last but not least, application of cellulose-based hydrogels and cross-linking mechanism was also discussed herein.

2 Synthesis and Properties of Hydrogel by Various Polymerization Reaction System

Based on the classification, hydrogels are divided into three groups: synthetic, natural, and hybrid (a combination of synthetic and natural) [2]. The raw materials used to synthesize these three groups of hydrogels are either hydrophilic monomers or hydrophobic monomers. Basically, synthetic polymers possess hydrophobic features in nature with a stronger chemical interaction as compared to natural polymers. Thus, the stronger bonding of synthetic polymers always shows a poorer degradation as compared to natural polymers, with a higher durability [2, 8]. Thus, the challenges to develop hydrogels with both biodegradability and durability are the key requirements for various market demands. Various types of hydrogel preparation techniques are reported to cater to the desirable property range of hydrogels, which includes (i) chemical cross-linking, (ii) physical cross-linking, and (iii) other newly emerging technologies [6]. These processes involve the cross-linking of natural/synthetic polymer chains by different interaction such as electrostatic forces, hydrogen bonds, covalent bonds, hydrophobic interactions, or chain entanglements. The

Table 1 Examples of polymers, initiator, and cross-linkers for hydrogel production

Synthetic [12]	**Natural** [13, 14]
Poly(hydroxyethyl methacrylate) (PHEMA) Poly(vinyl alcohol) (PVA) Poly(ethylene glycol) (PEG) Poly(acrylic acid) (PAA) Poly(methacrylic acid) (PMAA) Polyacrylamide (PAM)	Alginate, fibrin, agarose, chitosan, gelatin, silk, carrageenan, hyaluronic acid, collagen, cellulose, protein/peptides, dextran, matrigel, starch
Initiator [15–19]	
Ammonium persulfate Benzoyl peroxide Ammonium persulfate-tetramethylethylenediamine (APS-TMEDA) Ammonium persulfate-sodium sulfite-Mohr's salt 1-[4-(2-hydroxyethoxy)-phenyl]-2-hydroxy-2-methyl-1-propane-1-one (Irgacure D-2959)	
Cross-linker [11, 20, 21]	
N,*N*′-methylenebisacrylamide (MBAm or MBAA) Pentaerythritol tetraacrylate (PETRA) Ethylene glycol dimethylacrylate (EGDMA) Ethylene glycol diacrylate (EGDA) Poly(ethylene glycol) diacrylate (PEGDA) Ethylene glycol dimethacrylate (EGDMA)	

cross-linking is a stabilization process of liquid polymers, where the freely flowing chains were turned into multidimensional polymeric network in the form of a gel. In general, hydrogel preparation usually involved the use of material, such as monomers/polymers, initiator, and cross-linker (Table 1). The presence of water or other aqueous solutions acts as diluents, in order to control the heat generated during polymerization and tuning the final properties of hydrogels. Additional purification step is required to remove impurities (e.g., unreacted monomers/polymers, initiators, cross-linkers, by-products) especially for chemical synthesis process [11].

2.1 Chemical Synthesis Methods

Chemically cross-linked hydrogels are known as permanent or chemical gels, where the polymeric network is formed via the covalently cross-linked of monomers precursors/polymer chains. The chemical gels reached an equilibrium swelling state under optimized polymer-water interaction parameter and the cross-link density. Thus, chemical gels are considered as 'strong gels' with good mechanical strength and durability [6].

In general, the formation of chemical cross-linkage in chemical gel involves grafting of monomers on the backbone of the polymers or usage of a cross-linking agent to interact between polymer chains. The interaction process occurred either by (i) reaction between activated functional groups of natural/synthetic polymers (e.g., –OH, –COOH, and $–NH_2$), (ii) using small molecular weight of cross-linker

(e.g., formaldehyde, epoxy compounds, dialdehyde), (iii) using photosensitive agents (e.g., gamma and electron beam polymerization), and (iv) initiation with an enzyme [5, 22]. All the mentioned chemical polymerization approaches are categorized into three groups, which included aqueous solution polymerization, inverse-phase suspension polymerization, and irradiation polymerization (Table 2). The differences among the above polymerization approaches are listed in Table 3.

2.2 Physical Synthesis Methods

Physically cross-linked hydrogels are known as reversible or physical gels. It is present in three-dimensional network via polymeric molecular entanglements and/or secondary interaction including ionic, hydrogen force or hydrophobic interactions. Physical gels are divided into two groups, which are strong physical gels and weak gels. The strong gels provide permanent physical interaction between polymer chains under certain experimental conditions. It shows similar characteristics as chemically cross-linked gels. Examples of strong physical bonds are lamellar microcrystals, glassy nodules, or double and triple helices. In contrast, physical gels with temporary connections between polymeric chains can lead to a reversible process. This cross-linkage leads to finite lifetimes of products and continuously restructuring ability. Examples of weak physical bonds are hydrogen bond, block copolymer micelles, and ionic associations [2, 6].

Generally, the dissolution of physical gel is inhibited by physical interaction between polymer chains without the presence of cross-linking agents. Some of the cross-linking agents contain toxicity which affect the purity of substances (e.g., drugs, cell, proteins, etc.) to be entrapped in gels, as well as the need for further removal before application, particularly in the food and personal care industries. However, these physical interactions are reversible, which are easily decomposed under the physiological environment (such as temperature, pH, or electric field) or application of stress. Thus, the physical gels are considered biodegradable and biocompatible [5]. There are several methods for the preparation of physically cross-linked hydrogels, which include crystallization, amphiphilic graft and block copolymers, ionic interaction, complex coacervation, hydrogen bonding, and protein interaction. The roles and examples of physical hydrogels are summarized in Table 4.

2.3 Newly Emerging Approaches

The existing technology for hydrogel production, such as cross-linking copolymerization, cross-linking of reactive polymer precursors, and cross-linking via polymer-polymer reaction, is still rendering limited criteria during the process and features of hydrogels. Several studies have reported difficulty in controlling the detailed structure (chain length, sequence, and three-dimensional structure) due to the presence of side reaction, and unreacted pendant groups and entanglements occur. In addition,

Table 2 Methods for different chemical cross-link hydrogels

	Methods	Roles	Examples	Reference
1.	Aqueous solution polymerization	Reaction between ionic and neutral monomers with multifunctional cross-linking agent Polymerization is initiated thermally by UV irradiation or redox initiator system Aqueous solvent serves as heat sink for polymerization process (e.g., water, ethanol, water-ethanol mixtures, and benzyl alcohol)		
(a)	Radical polymerization	Known as chain-growth polymerization or anionic or cationic polymerization The process involves initiation, propagation, and termination steps Generation of free-radical activities induces the addition of monomers in polymer chains	Poly(*N*-isopropylacrylamide) Poly(sorbitan methacrylate) Poly(*N*-vinyl-2-pyrrolidone)	[23] [24] [25]
(b)	Chemical reaction of functional groups	The cross-linking involves functional group (–OH, –COOH, $–NH_2$) of hydrophilic polymers with polyfunctional cross-linking agents		
	(i) Aldehydes	Hydrophilic polymers having –OH groups form cross-link through cross-linking agents – aldehydes (e.g., glutaraldehyde)	Polyvinyl alcohol (PVA) cross-linked with glutaraldehyde hydrogels	[26]
	(ii) Addition reaction	Bis or higher-functional cross-linkers may be used to react with functional groups of hydrophilic polymers through addition reactions	Cross-linking glycidyl methacrylate derivatized dextran (Dex-GMA) and dithiothreitol (DTT)	[27]
	(iii) Condensation reaction	Reaction occurs between the functional group of –OH and $–NH_2$ with carboxylic acids or derivatives to form polyesters and polyamides	Zinc phthalocyanine-PEG-alginate copolymer	[27]

(*continued*)

Table 2 (continued)

	Methods	Roles	Examples	Reference
(c)	Enzyme-induced cross-linking	Enzymes act as a catalyst in cross-linking by cleave or form a chemical bond with polymer chains without interference with other chemical functional groups in polymer molecules For example, horseradish peroxidase, transglutaminase, tyrosinase, phosphopantetheinyl transferase, and lysyl oxidase	Enzymatic cross-linking of a nanofibrous multidomain peptide hydrogel	[28]
2.	Inverse-phase suspension polymerization	Monomers and initiator are dispersed in the nonpolar solvent (e.g., *n*-hexane, toluene) as a homogeneous mixture (water in oil system) Continuous stirring and utilization of low hydrophilic-lipophilic-balance (HLB) suspending agent/surfactant to maintain the dispersion of mixture The final hydrogel products present in the form of powder or microspheres (beads) with desirable sizes	Polymerization of highly hydrophilic monomers, such as salts of acrylic and methacrylic acids, as well as acrylamide For example, poly (methacrylic acid-co-partially neutralized acrylic acid) hydrogels prepared using SPAN 80 as the dispersant, heptane as the organic phase	[29]
3.	Irradiation polymerization	High-energy electromagnetic irradiations (e.g., gamma, x-ray, and electron beams) are applied as an initiator/cross-linker to induce the formation of radicals from hydrophilic polymer chains for the cross-linking process The process is initiator-free and render high purity of hydrogels	Gamma-radiation water-soluble polymer blends based on poly(vinyl alcohol) (PVA) and poly (ethylene glycol) (PEG)	[30]

Table 3 Comparison between three polymerization approaches

Polymerization type	Characterization
Microwave irradiation polymerization	High efficiency, fast heat, and clean (mass shape products)
Inverse-phase suspension polymerization	Higher costs, complex, and unstable (particle products)
Aqueous solution polymerization	Lower cost, easy control, and stable (mass shape products)

the produced hydrogels are of poor mechanical properties and slow or delay in response times to external stimuli [1]. Thus, process modification is necessary in order to control the polymerization and improve the characteristic of hydrogels (better mechanical properties, viscoelasticity). Several novel technologies for the hydrogel production were presented in Table 5.

3 Cellulose-Based Superabsorbent Hydrogels

Owing to the hydrophilic characteristic performance, superabsorbent hydrogels have a high capacity for water uptake, which can absorb, swell, and retain aqueous solutions up to hundreds of times from their own weight (dry sample). Since most of the superabsorbent hydrogels are produced from synthetic polymers (acrylics), the tendency for replacing these synthetics with greener alternatives is more than overwhelming due to the poor degradability and biocompatibility of synthetic superabsorbent [10]. Thus, as an alternative to a greener route, cellulose-based superabsorbent hydrogel was invented. Cellulose (abundant biomass, biocompatibility, biodegradable, nontoxic, low cost and renewable, abundant hydroxyl groups) can be used to produce superabsorbent hydrogels easily with fascinating structures and properties which will be discussed in detail in this section.

3.1 Cellulose Structure and Biodegradability

The biodegradability characteristic for cellulose has been broadly investigated because of its capacity of molecular weight reduction, lower mechanical strength, and high solubility aspect. The great biocompatibility of cellulose, cellulosic, and cellulose disintegration has provoked the extensive utilization of cellulose-derived materials in biomedical utilizations. Moreover, the chemical alteration and cross-linking of water-solvable cellulosic material with bioresorbable component are able to produce degradable, absorbable, and resorbable cellulose-derived materials. In addition, cellulose and its subordinates are ecologically well disposed, as they are degradable by a few microscopic and macroscopic organisms that are present in

Table 4 Methods for different physically cross-linking hydrogels

	Methods	Roles	Examples	Reference
1.	Crystallization	The gelation process involves the formation of microcrystals in the polymer structure due to the cycle of freeze-thawing	**By homopolymer systems**: Polyvinyl alcohol and calcium alginate gel rendered touch and elastic behavior after repeated freeze-thaw process **By stereocomplex**: The presence of stereoisomers with opposite chirality (e.g., L-lactic acid and D-lactic acid) with high molecular weight	[31] [32]
2.	Ionic reaction	Polymers with ionic groups formed cross-linking with the presence of di- or trivalent counterions (metallic ions) Cross-linking occur under mild condition: physiological pH and room temperature	Polyelectrolyte solution (e.g., Na^+ alginate$^-$) with a multivalent ion of opposite charges (e.g., Ca^{2+} and $2Cl^-$)	[33]
3.	Block and amphiphilic graft copolymers	Self-assemble characteristic for amphiphilic (both hydrophilic and hydrophobic) graft and block polymers The copolymers may consist of hydrophobic chains with hydrophilic grafts (or water-soluble polymer backbone)	Poly(lactide-co-glycolide) (PLGA) and polyethylene glycol (PEG) copolymers favor for drug delivery system PEG and polybutylene terephthalate (PBT) copolymers Hydrophobized polysaccharides (e.g., dextran, chitosan, carboxymethyl-curdlan, and pullulan)	[34] [35] [36]
4.	Hydrogen bonding	Formation of hydrogen bonding occurs between polymers carrying carboxyl groups (–COOH) Protonation favorable in low-pH condition	Hydrogen-bounded carboxymethyl cellulose (CMC) Carboxymethylated chitosan (CMC) hydrogels Xanthan-alginate Poly(acrylic acid)- and poly (ethylene oxide)-based hydrogel Poly(acrylic acid) (PAA) and poly(methacrylic acid) (PMAA) with polyethylene glycol (PEG)-based hydrogel	[36]

(*continued*)

Table 4 (continued)

	Methods	Roles	Examples	Reference
5.	Complex coacervation	The presence of the mixture of polyanion-polycation will form complex coacervate gels Polymers with opposite charges will tend to attract each other to form soluble and insoluble complexes under different concentrations and pH of respective polymer solutions	Polyanionic xanthan with polycationic chitosan Proteins below its isoelectric point are positively charged and likely to associate with anionic hydrocolloids and form polyion complex hydrogel	[37] [38]
6.	Protein interaction	Protein interaction involves block copolymers of Prolastin (consisted repetition of silk-like and elastin-like blocks) Prolastin is fluid solutions in water and form the gel under physiological conditions as the crystallization of the silk-like domains occurs	Genetically engineered proteins interaction Antigen-antibody interaction	[39] [40]

our surrounding [44], which can disintegrate cellulose into cellulose-specific enzyme (i.e., cellulase) [45].

3.2 Water-Soluble Cellulose Derivatives

Most of the water-soluble cellulose derivatives are obtained via the surface modification of cellulose with the etherification process (reaction between hydroxyl groups of cellulose with the organic compounds, e.g., methyl and ethyl units). Subsequently, cellulose-based hydrogels are either reversible or stable, which can be formed by cross-linking between aqueous solutions of cellulose ethers, such as methylcellulose (MC), hydroxypropyl methylcellulose (HPMC), ethyl cellulose (EC), hydroxyethyl cellulose (HEC), and sodium carboxymethylcellulose (CMCNa), which are among the most widely used cellulose derivatives. The chemical structure of such derivatives is shown in Table 6. It is worth highlighting that all these polymers have shown a wide application as thickeners and/or emulsifying agents in the food, pharmaceutical, and cosmetic industries, due to their non-toxicity and low cost. Water-soluble cellulose derivatives are mostly biocompatible which can be used as thickener, binding agents, emulsifiers, film formers, suspension aids, surfactants, and more. They have been used to fabricate cellulose-based hydrogels through physical cross-linking, chemical cross-linking, and irradiation cross-linking which have been discussed above.

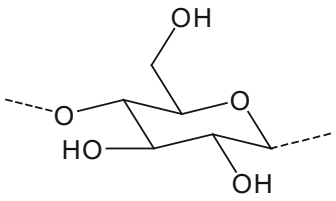
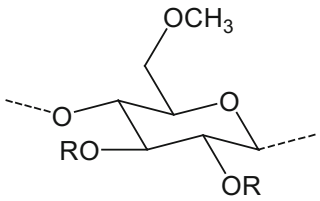
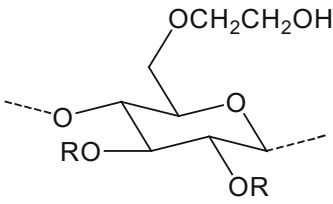
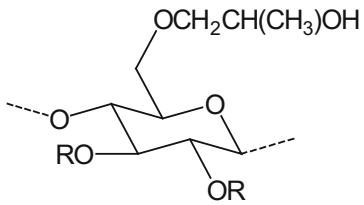
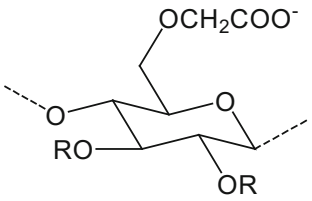
Table 5 Methods for different novel technologies

Methods	Roles	Examples	Reference
Solid-liquid interface technology	Polymerization occurs by immersed agarose gel rod loaded with acetic acid in the cellulose solution, to form onion-like and multilayered tubular cellulose-based hydrogels Controllable size, layer thickness, and interlayer space of the multilayered hydrogels Hydrogels render good architectural stability, solvent resistance, high compressive strength, and excellent biocompatibility	Multilayered tubular cellulose hydrogels	[41]
Electrospinning technique	Well-aligned, highly ordered, and covalently cross-linked polyacrylamide (PAM) hydrogel microfiber produced by using electrospinning techniques This technique is able to generate ordered structures from nanoscale to microscale fibers for biological muscle application	Highly aligned and covalently cross-linked polyacrylamide hydrogel microfibers	[42]
Microwave technology	Cross-linking approach assisted by microwave led to strong irradiation penetrating ability, faster heating, and a cleaner process Poly(vinyl alcohol) with either poly(acrylic acid) or poly (methyl vinyl ether-alt-maleic anhydride) forms cross-linking without the use of monomers, thus avoiding the purification step of unreacted species	Combination between poly (vinyl alcohol) with either poly(acrylic acid) or poly (methyl vinyl ether-alt-maleic anhydride)	[43]

3.3 Cellulose-Based Hydrogels and Cross-Linking Strategies

Hydrogels can be divided into those formed from natural polymers and those formed from synthetic polymers. On the basis of the cross-linking method, the hydrogels can be divided into chemical gels (covalent bond), physical gels (molecular self-assembly through ionic or hydrogen bonds), and irradiative cross-linking (formation of covalent bonding between polymer chains).

Table 6 Chemical structure of soluble cellulose derivatives

Cellulose 	Methylcellulose (MC) 
Hydroxyethyl cellulose (HEC) 	Hydroxypropyl methylcellulose (HPMC) 
Carboxymethyl cellulose (CMC) 	

3.3.1 Physical Cross-Linking of Cellulose Derivatives

In the family of thermos-reversible gelling polymers for hydrogels, hydrophobically modified cellulose is one of the largest members. When hydroxyl groups are substituted partly by methyl groups or hydroxypropyl groups, some hydrogen bonds are prevented, and the resultant derivatives become water soluble [46]. Methylcellulose (MC) aqueous solutions possess the unusual properties in forming reversible physical gels, due to hydrophobic interactions when heated above a particular temperature [47]. On the other hand, hydroxypropyl methylcellulose (HPMC) has a higher gelation temperature than MC, which forms firmer gels with equivalent substitution and molecular weight. Evidence have indicated that the gelation of HPMC cellulose derivatives resulted from the removing of water molecules from methoxylated regions of the polymer [48]. Sammon's group [48] successfully modified hydroxypropyl methylcellulose with 9.1% hydroxypropyl and 29.3% methoxyl at 4 °C for 24 h. In addition, Sekiguchi et al. [49] discussed the hydrophobic interactions and hydrogen bonds contributed to thermally reversible

gelation of methylcellulose aqueous solution. They were successfully modified cellulose acetate with dimethyl sulfoxide (DMSO) under a reaction condition of 60 °C and 1-h process. Subsequently, the sample underwent the methylation process (methylene chloride) and was further washed with deionized water.

As reported by Joshi et al. (2008), methylcellulose (MC) in cold deionized water shows a higher gelation rate at higher concentrations by using heating-cooling cycles. Initially, dried methylcellulose mixed with deionized water and heated till the temperature at 95 °C. The sample was allowed to cool down to 22 °C for at least 24 h, and finally the sample was maintained at a temperature of 4 °C. As a result, the gelation rate during the second heating-cooling cycle is higher than that in the first cycle [50].

Hydroxypropyl methylcellulose (HPMC) is a methylcellulose modified with a small amount of propylene glycol ether group attached to the anhydroglucose of the cellulose. Weiss' group [51] has developed a series of biomaterials based on HPMC. The first generation of injectable calcium phosphate ceramic suspensions is composed of a mixture of HPMC solution and biphasic calcium phosphate granules. The aggregation and gelation behavior of HPMC (19–24% methoxyl and 7–12% hydroxypropyl) aqueous solutions is concluded as follows: (i) polymer reputation increases due to thermal motion, which led to a weaker network; and (ii) above 55 °C, the polymer chains become more hydrophobic, and polymer clusters start to form [52].

The second generation of hydrogel products that can suppress the long-term flow by easily controlling the cross-linking of silated HPMC (Si-HPMC) has been developed by Vinatier's group [53] in 2009. Basically, Si-HPMC powder was solubilized in NaOH for 2 days. The solution was then sterilized by steam (121 °C, 30 min). To allow the formation of a reticulated hydrogel, the solution was finally mixed with *N*-(2-hydroxyethyl)piperazine-*N*′-(2-ethanesulfonic acid) (HEPES) buffer. The resulted Si-HPMC is nontoxic and biocompatible so that it can be widely used in biomedical areas, such as scaffolding for cell culture and cartilage model, and implanted in bone defects [54]. In addition, Si-HMPC-based hydrogels are developed as a scaffold for the 3D culture of osteogenic cells, which would be suitable for both in vitro culture and in vivo injection. The results from the mineralization assay and gene expression analysis of osteoblastic markers and cytokines indicate that all of the cells cultured in 3D into this hydrogel exhibit a more mature differentiation status from cells cultured as a monolayer on plastic. This Si-HPMC hydrogel is well suited to support osteoblastic survival, proliferation, and differentiation as it is used as a new scaffold and represents a potential basis for an innovative bone repair material [55].

3.3.2 Chemical Cross-Linking of Cellulose Derivatives

The stable structure and effective swelling of cellulose-based hydrogels often require a chemically cross-linked network. Some difunctional molecules are employed as the cross-linker for cellulose or its derivatives to covalently bind different polymer molecules in a three-dimensional hydrophilic network [46].

Sannino et al. [45] exploited the superabsorbent hydrogels based on cellulose through cross-linking carboxymethyl cellulose (CMC) and hydroxyethyl cellulose (HEC) with a cross-linking agent such as divinyl sulfone (DVS). Then sodium hydroxide (NaOH) and poly(ethylene glycol) (PEG) which acted as spacers between cross-links were added into the solution. These polyelectrolyte hydrogels display a high sensitivity in sorption capacity with variations of the ionic strength and pH of the external solution. Besides, the superabsorbent hydrogels are also developed to treat edemas for body water elimination. If hydroxypropyl cellulose (HPC) hydrogels are synthesized at certain temperatures in the single-phase regime, they remain nonporous, whereas when cross-linked in the biphasic regime, it will turn to microporous structure. Additionally, Hirsch and Spontak [56] reported the dynamic mechanical properties and swelling capacities of these hydrogels as a function of cross-linking temperature. The results showed that the HPC hydrogels when cross-linked with ammonia (NH_3) and epichlorohydrin (ECH) had excellent ability to absorb anionic dye with maximum adsorption capacity of 2478 (g/kg) which can be achieved at pH 3.96.

In 2008, Demitri et al. [57] reported the preparation of HEC and CMCNa hydrogels with citric acid as a cross-linker, which can overcome toxicity and material costs, as compared to divinylsulphone or with a carbodiimide cross-linking agent. Briefly, CMCNa and HEC (3:1) were mixed with citric acid which acts as a cross-linking agent. Results indicated that the swelling ratio of hydrogels depends on the reaction time and citric acid concentration, when the swelling degree reaches 900 with 3.75% of acid.

3.3.3 Irradiative Cross-Linking of Cellulose Derivatives

Irradiation is a useful method for the formation of covalent bonding between polymer chains. This method is advantageous because of the high purity of the hydrogel product without the use of toxic cross-linkers, thus enlarging the applications in food and pharmaceutical industries. However, only a small fraction (17–30%) of gel aggregates (lumps) can be obtained by γ-ray irradiation at a dose of 20 kGy from 20 wt% of biopolymer solutions (such as cellulose/ionic liquid/water, CMC, and carboxymethyl chitosan (CMCT) aqueous solutions), with the assistance of generated hydroxyl radicals [58, 59].

The electron beam (EB) irradiation in the vacuum seems to be able to increase the gel yield (the gel fraction reached up to 55% at 20 kGy and increased with the irradiation dose). Petrov group [60] successfully obtained an opaque spongy material via UV irradiation from 3 wt% of aqueous cellulose polymers (HPMC, HEC, and MC) with (4-benzoylbenzyl) trimethylammonium chloride (BBTMAC) as a photo initiator. At high energy doses and low polymer concentration (10 wt%), the degradation of the polymer chains competes with cross-linking, thus resulting in the destruction of network structure and a decrease in tensile strength. The occurrence of degradation was due to EB irradiation (higher radical number created in the system) or irradiation in an oxygen-free atmosphere to avoid the generation of oxides and peroxides.

4 Stimuli-Responsive Cellulose-Based Hydrogels

The smart hydrogel can be categorized as physical or chemical stimuli-responsive hydrogels. Physical stimuli (temperature, electric or magnetic fields, and mechanical stress) will affect various energy sources and alter molecular interaction at a critical onset point. However, the chemical stimuli (pH, ionic factors, and chemical agents) will change the interaction between polymer chains and solvent at the molecular level. Thus, the responsive cellulose-based hydrogels found a new generation of smart materials to be used in numerous fields (biomedical devices, scaffolds for engineered tissues, biosensors, and actuators).

4.1 pH-Responsive Hydrogels

pH-responsive hydrogels are produced of polymeric backbones with the ionic pendant groups that can accept or donate protons in response to an external pH change [46, 61]. The acid- or basic-side functional groups in polyelectrolytes undergo dissociation in a similar way as the acidic or basic groups of monoacids or monobases. The ionization on polyelectrolytes, however, is more difficult due to electrostatic effects of other adjacent ionized groups. So, the apparent dissociation constant (*K*a) may be different from that of the corresponding monoacid or monobase. When the macromolecules are constituted by a huge amount of ionizable groups, such polymer is called polyelectrolyte. Hydrogels constituted by polyelectrolytes are, often, sensible to pH changes, which makes the hydrogel to swell (if the side functional groups are in an ionized state) or to collapse (if the side functional groups are not ionized). The process of swelling/collapsing of pH-sensitive hydrogel is reversible and may have strong applications in the pharmaceutical field because hydrogels can protect a given encapsulated drug from hostile environments, e.g., the presence of enzymes and low pH in the stomach region. A drug that can suffer degradation at acidic conditions can be transported through the gastric tract and be released in the colon if it is encapsulated in an appropriated pH-sensitive hydrogel. Hydrogels can also control drug release by changing the gel structure in response to environmental stimuli. Hydration under alkaline pH favors enzyme access to the hydrogel and its later enzymatic decomposition with the ensuing delivery of the drug entrapped in the hydrogel [61].

4.2 Temperature-Responsive Hydrogels

Chemically cross-linked thermosensitive hydrogels undergo volume change rather than sol-gel transitions. Certain molecular interactions, such as hydrophobic associations and hydrogen bonds, play a vital role in the abrupt volume change of these hydrogels at the critical solution temperature. In a swollen state, water molecules form hydrogen bonds with polar groups of polymer backbone within the hydrogels

and organize around hydrophobic groups as iceberg water. At critical solution temperature, hydrogen bonding between the polymer and water, when compared with polymer-polymer and water-water interactions, becomes unfavorable. This forces the quick dehydration of the system, and water is released out of the hydrogel with a large gain in entropy, resulting in the shrinkage of the polymeric structure. Temperature-sensitive hydrogels will have a small variation in temperature which induces a phase transition, and therefore shrinking or expansion of the material is observed. This is because chemically cross-linked thermosensitive hydrogels undergo a volume change rather than sol-gel transitions. Theoretically, certain molecular interactions (hydrophobic associations and hydrogen bonds) play a vital role in the abrupt volume change of these hydrogels at a critical solution temperature. As a result, an abrupt transition in the 3D matrix occurs: water-solvated macromolecule quickly dehydrates and changes to a more hydrophobic structure.

4.3 Ionic Strength-Responsive Hydrogels

The swelling, loading, and releasing-solute capabilities of hydrogels are, sometimes, dependent on the ionic strength (IS) of the external fluid. Due to the diffusion and convection, an osmotic pressure is produced via the difference in the ionic concentration of the exterior solution and interior hydrogel, thus, causing the swelling and shrinking of the cellulose smart hydrogel [46].

4.4 Solvent-Responsive Hydrogels

The response to solvent is also a very important issue on stimuli hydrogels. Several aspects are exploited in this way. The change from hydrophilic to hydrophobic solvent (or the reverse) is a common strategy to induce the shrinking or expansion of a three-dimensional network [46].

4.5 Other Responsive Hydrogels

Other than stimuli-responsive cellulose-based hydrogel, there are a few different strategies for visible stimuli, for example, ultraviolet-visible, magnetic field, mechanical stress, and others to generate changes in hydrogels. As specified, a few frameworks have been produced to join more stimuli-responsive structure in the polymer systems [62]. As stimuli-responsive cellulose-based hydrogel is actively developing, there is a pattern in growing new smart hydrogel to be responsive not only to stereotype stimuli but also to machine and analytical device that have a more responsive characteristic.

5 Structure Property Relationships in Hydrogels

Generally, hydrogels consist mostly of 60–90% fluid and 10–30% polymer [63]. Due to its characteristic properties such as swell ability in the water, high water content and elastic nature similar to natural tissue, biocompatibility, and lack of toxicity, hydrogels have been utilized in a wide range of biological, medical, pharmaceutical, and environmental applications [64]. Moreover, to achieve a successful network of hydrogels, it must consider its chemical cross-linking, physical entanglement, ionic bond, and hydrogen bond [65]. In a broad sense, it shows that the hydrogels are categorized into chemical gels when the cross-links of hydrogen bonds in the main chains are replaced by the stable covalent bonds [66] and into physical gels when the links are held together by secondary weak bonds such as ionic bonds, hydrogen bonds, van der Waals and electrostatic interactions, or molecular entanglements [65, 67].

A different type of preparation method for hydrogels is another parameter to classify the hydrogels, which includes (i) homopolymer hydrogels, (ii) copolymer hydrogels, (iii) interpenetrating polymeric hydrogels, and (iv) multi-polymer hydrogels [7]. The homopolymer hydrogels referred to as polymer networks are composed only of one type of hydrophilic monomer, while the copolymer hydrogels are composed of two types of monomers, where at least one is hydrophilic monomers [7]. Meanwhile, the interpenetrating polymeric hydrogels are hydrogels that are prepared by swelling a network without any chemical bonds between them, such as a swelling process of polymer 1 in monomer 2, to make an intermeshing network of polymer 1 and polymer 2 [68]. Last but not least, the multi-polymer hydrogels indicate that hydrogels consist of a combination of more than three types of monomers [68]. Different types of hydrogel lead to different characteristic features, which included structure parameters, mechanical properties, and swelling effect.

5.1 Structural Parameters

Theoretically, several parameters of hydrogel structures are intensively discussed in many studies which are (i) polymer volume fraction in the swollen state ($V_{2,\,S}$), (ii) average molecular weight between cross-links (M_e), and (iii) correlation length (ξ) also known as the network mesh (or pore) size [68]. The equilibrium polymer volume fraction in the gel ($V_{2,\,S}$) is the ratio of the polymer volume (V_p) to the volume of the swollen (V_{gel}) and the reciprocal of the volume swelling ratio (Q):

$$V_{2,S} = \frac{V_p}{V_{gel}} = Q^{-1} \tag{1}$$

Besides, the polymer volume fraction in the swollen state can also be determined by the equilibrium swelling experiments when the average molecular weight between cross-links (M_e) is theoretically related to the degree of cross-linking (X):

$$(M_e) = \frac{M_0}{2X} \tag{2}$$

where M_0 is the molecular weight of the repeating unit of a polymer.

The correlation length or the network mesh size (ξ) indicates the distance between the consecutive junctions, cross-links, or tie points. All the network parameters can be measured through a range of experimental techniques or calculated by the application of the network deformation theory [68].

5.2 Mechanical Properties

At present, there are a few methods available for characterizing the mechanical properties of hydrogel constructs. The mechanical properties of hydrogels are very difficult to describe and understand its structure. Besides, its mechanical behavior can be studied by using theories to analyze its polymer structures and to determine the effective molecular weight between cross-links and to provide information about the number of elastically active chains and cyclization versus cross-linking tendency [68].

5.2.1 Dynamical Mechanical Analysis

The dynamical mechanical analysis is characterization method for hydrogels to provide information related to the viscoelastic behavior of hydrogels by measuring the response of a sample when it is deformed under periodic oscillation (stress or strain) [68]. Based on the dynamic experiment, the material is subjected to a sinusoidal shear strain (or stress):

$$\gamma = \gamma_0 \sin(\omega t) \tag{3}$$

where γ_0 is the shear strain amplitude, ω is the oscillation frequency (which can also be expressed as $(2\lambda\ gf)$ where f is the frequency in Hz), and t is the time. The mechanical response shows that the shear stress (σ) of viscoelastic materials is intermediate between an ideal pure elastic solid (in phase with the deformation) and an ideal pure viscous fluid (90° out of phase with the deformation). Therefore, it is out of phase with respect to the imposed deformation as expressed by:

$$\sigma = G^*(\omega)\, \gamma_0 \sin(\omega t + \delta p) \tag{4}$$

And consequently

$$\sigma = G^*(\omega)\gamma_0 \sin(\omega tg)\cos(\delta) + G''(g\omega)\, \gamma_0 \cos(\omega t)\sin(\delta) \tag{5}$$

and if it is defined

$$G' = G^* \cos(\delta)$$

$$G''(\omega) = G^* \sin(\delta) \tag{6}$$

we get:

$$\sigma = G'(\omega)\gamma_0 \sin(\omega t) + G''(g\omega)\,\gamma_0 \cos(\omega t) \tag{7}$$

where G′(ω) is the shear storage (or elastic) modulus and G″(ω) is the shear loss (viscous) modulus. G′ is referred to as the elasticity or the energy stored in the material during deformation, whereas G″ gives information about the viscous character or the energy dissipated as heat. The dependence of the elastic and viscous moduli upon frequency is called mechanical spectra. The combined viscous and elastic behavior is given by the absolute value of complex shear modulus G*:

$$\mathrm{B}^*(\omega) = \sqrt{\mathrm{G}'^2\mathrm{G}''^2} \tag{8}$$

or by the absolute value of complex viscosity η* defined as:

$$\eta^*(\omega) = \sqrt{\frac{\mathrm{G}'^2 + \mathrm{G}''^2}{\omega}} \tag{9}$$

On the other hand, the ratio between the viscous modulus and the elastic modulus is expressed by the loss tangent:

$$\tan\,\delta = \frac{G'}{G''} \tag{10}$$

where J is the phase angle. The loss tangent is a measure of the ratio of energy lost to the energy stored in the cyclic deformation.

Theoretically, the ratio between the stress and strain may depend both on time and stress. The ratio will only depend on time if the deformations are kept small in order to obtain a liner material behavior. To determine the region of linearity, the preliminary strain sweep tests at fixed oscillation frequency are performed. Specifically, the dynamic moduli are monitored while logarithmically varying the strain amplitude, γ_o.

5.2.2 Viscoelastic Properties

According to Borzacchiello et al. [68], the mechanical spectra analysis can clearly distinguish the concentrated (entangled) polymer solutions and gels based on the concentration and its frequency. For the concentrated solution at low frequency, the solution presents a viscous behavior ($G'' > G'$), while at high frequency, it shows an elastic behavior ($G' > G''$). The transition between viscous and elastic behavior is indicated by the cross point of G′ and Gil curves, as a function of frequency, occur at a given value of the frequency (f^*). Besides that, the common behavior of the concentrated solution when at low frequency shows that the solution behaves as a viscous liquid which the polymer chains are able to achieve the equilibrium configuration through the Brownian motion within the time scale of the experiment. Meanwhile, when at high frequency, the chains cannot be detached during the

short period of oscillation, and it behaves as a temporary cross-linked network to accommodate stress by network deformation and elastic behavior ($G' > G''$). The crossover frequency (f^*) depends on the intrinsic rate of disentanglement of polymer chains.

5.2.3 Stress-Strain Behavior

Hydrogels consist of a water-swollen network of cross-linked polymer chain which can be considered in a rubber state. This rubber state condition allows them to respond to external stresses with a rapid rearrangement of polymer segments. The mechanical stress-strain properties of hydrogels in this rubber-like behavior correspond mainly to the architecture of the polymer network. Besides, to generate an equation of rubber elasticity, the relationship of network characteristics, mechanical stress-strain behavior with the classical and statistical thermodynamics, and phenomenological approaches must be used and considered. Based on the classical thermodynamics, the state equation for rubber elasticity is shown below:

$$f = \left(\frac{\delta U}{\delta L}\right)_{T,V} + \left(\frac{\delta U}{\delta L}\right)_{L,V} \tag{11}$$

where f is the retractive force of the elastomer in response to a tensile force, U is the internal energy, L is the length, V is the volume, and T is the temperature.

Other than that, for elastomeric materials, the change in length is not internally driven by retractive forces. Indeed, for those materials, the bonds are not stretched with a change in L, but an increase in length will decrease the entropy due to the changes in the end-to-end distances of the network chains. The entropic model for rubbery elasticity is the most reasonable approximation for hydrogels while the entropy is full with 90% of the stress. The retractive force and entropy are related through the Maxwell equation:

$$-\left(\frac{\delta U}{\delta L}\right)_{T,V} = \left(\frac{\delta U}{\delta L}\right)_{L,V} \tag{12}$$

By expressing the retractive force using the statistical thermodynamics, it can be assumed there is no volume change upon deformation. The free energy change on straining the polymer chains is due to the restraints placed on the configurational rearrangements and is considered to be totally entropic in origin [8]. It is, therefore, possible to write the equation of state for rubber elasticity as follows:

$$\tau = \left(\frac{\delta A}{\delta \lambda}\right)_{T,V} = \frac{\rho RT}{\bar{M}C}\frac{\bar{r}_0^2}{\bar{r}_f^2}\left(\lambda - \frac{1}{\lambda^2}\right) \tag{13}$$

where τ is the shear stress per unit area, ρ is the density of the polymer, M_c is the average molecular weight between cross-links, and λ is the extension ratio. The quantity, $\bar{r}_0^2 / \bar{r}_f^2$, is the ratio of the end-to-end distance in a real network versus the

end-to-end distance of the isolated chains; it is generally approximated as 1 when it is unknown. From Eq. 13, it can be deduced that the stress is directly proportional to the number of network chains per unit volume (i.e., ρM_c). The equation assumes that the network is ideal in that all chains are elastically active and contribute to the elastic stress and network imperfections such as cycles, chain entanglements, and chain ends which are not taken into account [33–35]. To correct the chain ends:

$$\tau = \frac{\rho RT}{\bar{M}c} \frac{\bar{r}_0^2}{\bar{r}_f^2} \left(1 - \frac{2\bar{M}c}{\bar{M}n}\right)\left(\lambda - \frac{1}{\lambda^2}\right) \tag{13}$$

where M_n is the average molecular weight of the linear polymer chain before cross-linking. The correction can be neglected when $M_n \gg M_C$. From the constitutive equation, the modulus can be expressed as:

$$G = \frac{\rho RT}{\bar{M}c} \frac{\bar{r}_0^2}{\bar{r}_f^2} \left(1 - \frac{2\bar{M}c}{\bar{M}n}\right) \tag{14}$$

and the force per unit area as:

$$\tau = G\left(\lambda - \frac{1}{\lambda^2}\right) \tag{15}$$

The rubber elasticity theory predicts the nonlinear stress-strain behavior. The theory predictions describe the experimental results fairly well at low extension but are less accurate at higher elongations.

5.3 Swelling Properties

Swelling properties of hydrogels are important both dynamically and at equilibrium. The polymer chains in hydrogels can be obtained via either by physical or chemical stabilization of aqueous solutions, and thus, it is considered as one molecule regardless of its size [45]. A small change in environmental condition may trigger fast and reverse changes in the hydrogel. Hydrogels have the ability to sense changes in environmental parameters like pH, temperature, electric signal, and the presence of enzyme and other ionic species which may change the hydrogel physical texture. Apart from that, this swelling behavior of hydrogels can be determined by the several parameters which are the polymer volume fraction in the swollen state ($V_{2,\,S}$), the number average molecular mass between cross-links (Mc), and the mesh size (ξ) [69]. Besides, the equation of hydrogel volume in the dry state (V_d) and hydrogel volume when swollen to equilibrium (V_s) are shown below as (16) and (17), respectively:

$$V_s = \frac{m_{a,s} - m_{h,s}}{\rho_h} \tag{16}$$

$$V_d = \frac{m_a - m_h}{\rho_h} \tag{17}$$

where (m_a) is the mass of the initial dry polymer in air (m_h) is the mass of the dry polymer in a swelling medium, $m_{a,\ s}$ is the mass of the swollen hydrogel in the air after reaching equilibrium swelling, $m_{h,\ s}$ is the mass of swollen hydrogel in a swelling medium after equilibrium swelling, and ρ is the density of swelling medium. The mass of hydrogel in a non-solvent can be measured by placing the sample in a stainless steel mesh basket suspended in swelling medium before swelling measurements are made and after the equilibrium swelling is achieved. The polymer volume fraction of the hydrogel in swollen state ($V_{2,\ S}$) is calculated from the swelling data by using the following relationship:

$$\left(V_{2,S}\right), = \frac{V_d}{V_s} \tag{18}$$

where (V_d) is the volume of the dry polymer and (V_s) is the volume of the hydrogel after equilibrium swelling. The determination of swollen hydrogel volume (V_s) requires the placement of hydrogel sample in the buffer and allows it to attain equilibrium.

6 Synthesis and Characteristics of Cellulose-Based Smart Superabsorbent

Throughout the years, the "superabsorbent polymer" has been developed and widely used in various areas due to its extraordinary properties [70, 71]. Due to its superior characteristics such as excellent hydrophilic properties, high swelling ratio, and improved biocompatibility, this superabsorbent hydrogel shows a high potential to attribute in many industries such as sanitary, agriculture, biomedical, food packaging, pharmaceuticals, and others [72, 73]. Generally, most of the superabsorbent hydrogels are produced from synthetic polymers (acrylics acid), and for the past several years, researchers have focused its attention to replace synthetic polymers with "greener" alternatives due to poor degradability and biocompatibility of the synthetic superabsorbent [10]. Cellulose is one of the carbohydrate polymers with the most inexhaustible resources on Earth. This type of biopolymer is biocompatible, biodegradable, and nontoxic and is a low-cost material. Besides, cellulose consists of an abundance of hydroxyl groups that will interact between the hydrogen bond, which contributes to the cellulose's mechanical strength, molecular structures, and its properties [10]. Additionally, the advantages of cellulose-based superabsorbent hydrogels give superior characteristics such as high absorbency, high strength, good salt resistance, excellent biodegradable ability and biocompatibility, and other special functions that promise a wide range of applications in many fields [10, 65].

According to Sannino et al. [45] and Fekete et al. [74], the superabsorbent hydrogels were synthesized by both chemical and physical methods. The chemical

method involves the synthesis processing of cellulose-based superabsorbent hydrogels via covalent linkages, and this includes aqueous solution polymerization, inverse-phase suspension polymerization, and even microwave irradiation pathways [3]. Most of the cellulose-based superabsorbent hydrogels are synthesis via aqueous solution polymerization due to lower production cost, better control for heat of polymerization, and more convenience as compared to other methods. Besides, this method is mainly attributed to free-radical-induced polymerization, which monomers are polymerized through the action of initiators in the aqueous medium condition that is safe and harmless [10]. Other than that, the physical synthesis methods refer to the molecular assembly cross-linked by hydrogen bonds or ionic bonds between the polymers or by the interaction between the polymers. These physical cross-link techniques include freeze/thaw cycle technology and hydrogen bond cross-linking, which are also adapted in some cases [75]. Among the methods that are used for the preparation of cellulose hydrogels, physical approach is the best choice of process due to its simple pathway with zero solvent for environmentally friendly purposes [10].

7 Synthesis and Applications of Macro- and Nano-hydrogels

7.1 Synthesis Routes of Macro- and Nano-hydrogels

Recently, the synthesis of hydrogels by using biocompatible/biodegradable polymers in macro- and nanometer range is getting much attention. Among the research conducted are for the application in catalysis, electronics, bio-sensing, drug delivery, and nano-medicine [76]. The incorporation of nanoparticles or macro-particles with various structures and morphologies into the polymeric hydrogel matrix can be considered as a facile and effective way to obtain enhanced characteristics of hydrogels, which is similar to the particle strengthening effect in polymer bulk matrix [77]. For instance, the macro- and nano-sized hydrogels produced a higher area/volume ratio that significantly modifies the mechanical, thermal, and catalytic properties. As reported by Feeney et al. [78], under IUPAC classification, the micro-hydrogel is defined as a particle of hydrogel of any shape with an equivalent diameter of 0.1 to 100 μm. For nano-hydrogel, it is defined as a particle of hydrogel of any shape with an equivalent diameter of 1 to 100 nm. Generally, micro- and nano-hydrogels can be produced by several methods such as self-assembling, suspension, emulsion, precipitation or dispersion polymerization, micro-molding, droplet generation, microfluidics, and others [76].

7.2 Potential Application Fields

According to the Global Industry Analysts, Inc. report, the global superabsorbent hydrogel consumption was around 2.3 million metric tons in 2015, and it is expected that the global demand will continue to rise and reach 3.48 million metric tons in

2020 [79]. The rapid growth and demand for hydrogels were reflected on the developing markets and its different applications. On the other hand, Transparency Market Research reported that the global superabsorbent hydrogel market was valued at US$ 10084.9 million in 2016 and was predicted to reach US$ 17487.6 million by 2024. This large market suggests a strong tendency to develop novel superabsorbent hydrogel materials with higher water absorbency and excellent mechanical properties. This section discusses about the highly potential applications of cellulose-based superabsorbent hydrogels, which range from the conventional use of hydrogels in agriculture and personal health care to the more innovative biomedical applications. In fact, there are a number of hydrogel products that have either been commercially available or are in the progress of development. Cellulose-based superabsorbent hydrogels act as promising biomaterials for hydrogel products which show the greatest significance for various fields of application and thus are extensively studied in industrial and academic research.

7.2.1 Agriculture and Horticulture

Hydrogels have been widely proposed over the last 40 years for agricultural and horticulture usage. There is an increasing interest in using superabsorbent hydrogels in agriculture and horticulture due to several reasons, which includes ameliorating the water availability for plants, increasing the water holding properties of growing media (soilless or soils substrates), optimizing the water resources, and reducing the water consumption. Due to its unique properties, several possible agricultural applications of hydrogels have been defined.

During the swelling of hydrogel, it turns the glassy material to a rubber-like state, which is able to store water even under compression. However, the swollen hydrogel can slowly release its absorbed water via a diffusion-driven mechanism when there is a humidity gradient between the outside environment and the inner part of the material. Generally, the water molecules loaded in the polymer network can be released in a sustained and controlled manner through diffusion. In order to make the cultivation possible in the arid, desert, and drought-prone areas (especially in South America, Africa, and west of Asia), where there is always a lack of sufficient available water resources, the dry hydrogel (i.e., xerogel) which is in the form of granules or powder is envisaged to be mixed with the soil in proximity of the plant root area. In addition, the hydrogel is possibly charged with the plants, pharmaceuticals, or nutrients [45]. When the cultivation is watered (by either rain or irrigation), the water is absorbed and retained by the water, which can avoid the rapid water loss after watering due to drainage and evaporation. When the soil is in dried condition, the hydrogel will release the stored water and loaded nutrients in a continuous manner via diffusion mechanism as needed, keeping the soil or the substrate in the humid state over long periods of time [57]. On the other hand, this process allows a high saving of water as well as the redistribution of the water resources that is available for cultivation in other applications. A further advantage of using this novel material in the agricultural application is related to its swelling effect in the soil. Basically, the dry form of hydrogel granules which is almost similar in size with the

substrate granules is able to increase in size after swelling, thus increasing the soil porosity and providing a better oxygenation to the plant roots.

Unfortunately, most of the acrylate-based superabsorbent products available in the market are non-biodegradable, and some concern about toxicity was raised for agriculture application [57]. This is harmful to cultivation and human consumption; thus, it should be avoided. As a result, the concern of the public and researchers toward the biological system and environment issues has led to an increase in demand for cellulose hydrogel-based products. Several studies have been conducted toward the manufacturing of biodegradable nature hydrogel-based superabsorbent. So far, the development of environmentally friendly cellulose-based hydrogels fits perfectly in the current trend as an alternative to replace the conventional acrylate-based superabsorbent hydrogels. Such studies have been conducted and patented by Sannino and coworkers [80, 81], in which degradable cellulose-based superabsorbent hydrogels have been successfully invented. It is worth mentioning that the obtained hydrogels exist in the form of powder or a well-defined-shaped bulky material with the strong memory of its shape after swelling. Such hydrogels are capable of absorbing up to 1 l of water per gram without releasing it under compression and are able to charge with nutrients and to be released under a controlled kinetic [82]. Researches on the development of novel and green superabsorbent hydrogels for agriculture and horticulture have been further extended to recent years. In 2014, Li et al. [83] studied the effects of superabsorbent polymers on a soil-wheat (*Triticum aestivum* L.) system as a soil additive to increase crop yield and reduce the loss of soil water. The authors investigated the changes of crop yield, soil microbial activity, and water content between the modified soil and original soil; the results showed that the addition of superabsorbent hydrogels into the soil is able to improve the soil conditions with better crop yield and reduced detectable adverse effects on the soil microbial community. Besides that, Demitri et al. [57] proposed that the use of large-scale hydrogel might have an innovatory impact on the optimization of water resource management, especially in the agriculture field. The preliminary results revealed that the produced polyelectrolyte cellulose-based hydrogel could significantly increase the water retention capability of the soil and allow for the continuous release of water for a prolonged time effectively; thus, no additional watering is needed for the plants and soil. In fact, the proposed hydrogel potentially acts as an efficient storage and water reservoir in agriculture. A similar finding has been supported by Salmawi et al. [84], in which the superabsorbent hydrogel produced from acrylic acid and carboxymethyl cellulose with clay montmorillonite by gamma irradiation showed a higher percentage of swelling in distilled water and could act as a water-managing material in dried and drought-prone areas.

Pesticides are the most cost-effective way to control the growth of pest and weed. It is known that the cellulose-based superabsorbent hydrogels are used as pesticide carriers for special interest in terms of both sustainable and economic development. Hydrogels can be impregnated with fertilizer components such as nitrogen compounds, potassium ions, and soluble phosphate. Encapsulating the pesticides or herbicides into the cellulose-based superabsorbent hydrogels could be used to reduce the release rate of these herbicides [85]. This is because the chemical trapped

in a polymer network is normally unable to wash out immediately by water but is gradually released into the root zone before being absorbed by plants. Compared to those of conventional polymers such as poly(acrylic acid), polyacrylamide, polymethacrylic, cross-linked poly(vinyl alcohol), pectin, chitosan, and carboxymethyl cellulose, which normally have severe limitation such as rapid biodegradability in soil, cellulose-based superabsorbent hydrogel is able to increase the water capacity of soil, at the same time minimizing the water loss through evaporation and seepage [86]. In the mixture with other active substances, it can be used as the polymer matrix to transfer bioinsecticides or herbicides, which is mainly designed to control, for example, proliferation of insect larvae into the soil. In general, the superabsorbent and fertilizers are combined via two methods, which have been well described in the literature [87, 88]. In the first approach, fertilizers are blended with cellulose superabsorbent hydrogels. In the second methodology, fertilizers are added to the reaction mixture and polymerized in situ in order to be entrapped in the superabsorbent. Results verified that these two procedures always result to a higher release rate.

Furthermore, the role of hydrogels as horticultural substrates enhances the soil water capacity. During rainfall or irrigation, the hydrogels bind the water in the soil to prevent it from seeping into deeper layers [89]. Up to date, researchers have proposed the combination of inorganic clays, such as bentonite, kaolin, montmorillonite, etc., into pure cellulose superabsorbent hydrogels with the intention of improving the hydrogel strengths and swelling property and reduced production costs. In recent years, a study conducted by Bortolin et al. [90] has proven that polyacrylamide/methyl cellulose/montmorillonite nanocomposite superabsorbent hydrogels have presented a synergistic effect by rendering high fertilizer loading and the slow release of fertilizers. The results revealed that the produced cellulose-based hydrogels effectively reduced the loss of nitrogen by volatilization of ammonia.

In summary, the main advantages of cellulose superabsorbent hydrogels are controlled by the release of water, increase of soil porosity, long time maintaining soil humidity, and better oxygenation of plant roots. On the other hand, this type of hydrogels is biodegradable and low cost, has high holding capacity, and is an eco-friendly resource. Its application helps to reduce irrigation water demand, minimizes the plants death rate, increases the growth rate of plant and improves fertilizer retention in soil [91, 92].

7.2.2 Personal Health Care

Superabsorbent polymers have been introduced for various hygienic applications such as disposable diaper and feminine napkin industry for about 30 years ago due to their excellent water retention and the ability to retain the secreted liquids under pressure. In 1978, the commercial production of superabsorbent polymers began in Japan for the production of feminine napkins. This is considered to be the first generation of commercial superabsorbent hydrogels that has been successfully marketed [3]. Previously, the commercial superabsorbent hydrogels were made through alkaline hydrolysis of starch-graft-polyacrylonitrile in the 1970s. However,

Table 7 Water absorbency of different types of common absorbent materials [93]

Absorbent material	Water absorbency (wt%)
Superab A-200	20,200
Cotton ball	1890
Wood pulp fluff	1200
Soft polyurethane sponge	1050
Facial tissue paper	400
Whatman No. 3 filter paper	180

the high expenses and inherent structural weakness (lack of sufficient gel strength) had contributed to the major factors of its market defeat [93]. Further development of superabsorbent materials is being employed in baby diapers in France and Germany in the 1980s. In 1983, the low-fluff diapers which contained about 5 g super-absorbent polymers were launched. This was followed by the introduction of superabsorbent diapers with a thinner layer in several Asian countries, Europe, and the United States. The thinner layer of diapers and nappies was mainly due to the replacement of bulkier cellulose fluff with superabsorbent polymers that can retain much liquid more effectively [94].

Continuous development of superabsorbent materials has led to a new generation of high-performance diapers. It was worth noting that the diapers not only become thinner but have also improved the retention performance significantly which has proven to be beneficial in reducing diaper rash and leakage [45]. The results showed that premium diapers have the leakage values below 2%, while the average weight of a typical medium-size diaper was further decreased by 50%. This was advantageous in terms of economic sense and environmental issues due to the reduced packaging cost. Compared to superabsorbent polymers, traditional absorbent materials (such as polyurethane sponge and tissue papers) will not be able to hold most of the absorbed water when these materials are squeezed. As a result, superabsorbent polymers caused a huge revolution in the personal health-care industries over these years. Table 7 shows the water absorptiveness of some common absorbent materials using the commercially available superabsorbent polymers.

Making recyclable and disposable products such as napkins, diapers, hospital bedsheets, and sanitary towels is one of the important targets for the modern industry due to environmental awareness of society. Therefore, an innovative idea to this issue has recently been proposed, which involves the production of cellulose-based hydrogels with fully biodegradable properties. At present, the superabsorbent hydrogels contained in sanitary napkins are mostly derived from polymerized acrylamide or acrylic acid, which is a costly process, and the final product is environmentally unfriendly and poorly degradable [10]. Due to these reasons, some novel types of hydrogels composed of a mixture of hydroxyethyl cellulose and sodium carboxymethyl cellulose cross-linked with divinyl sulfone have been innovated. This hydrogel material is able to swell like conventional superabsorbent polymer, which exhibits higher water retention under centrifugal loads and swelling kinetics due to the capillary effects and the resulted introduction of microporous structures into hydrogel [45].

In order to establish more innovative methods for developing novel and new hydrogel products, many attempts have been made, which possess better swelling capabilities and are able to retain more fluids absorbed under the existence of external pressure or applied restraining force. Liu et al. reported a novel tactics for the production of eco-friendly superabsorbent hydrogels incorporated with flax yarn waste for sanitary napkin applications [95]. Their study proved that the product obtained exhibits from several outstanding properties such as excellent biodegradability, superabsorbent, and good in retention of artificial blood solution as compared to the currently commercialized, marketed sanitary napkin products. A similar study has been reported by Zhang et al., in which a flax cellulose-based superabsorbent composite was synthesized by the free-radical graft copolymerization of acrylic acid and acrylamide [96]. The results revealed that the yielded composite material attained the best water absorbency of urea. Most importantly, they found that 46.6% of the remaining residue after buried in soil after 90 days presented an excellent biodegradability. In modern times, a lot of convenient and comfortable disposable health-care products made up of hydrogels have been reported in literature; however, biodegradable health-care products have either not been commercially available or been industrialized [10]. In reality, more than 90% of superabsorbent composites are landfilled or incinerated after usage. This will cause serious environmental problems, undesirable water-keeping capacity, and higher cost that limit its practical applications [97]. Hence, continuous effort needs to be done in order to convert the cellulose-based superabsorbent hydrogels into the core layer of health-care products.

Further developments in the personal health-care area are expected with the formulation of the superabsorbent hydrogel materials containing enzymes and other additives in order to prevent unpleasant smells or infections. Furthermore, considering the scale of production of these materials is prerequisite as there is a clear need for environmentally friendly hygiene products that undergo biodegradation. Thus, it has a high value in the development of novel, green superabsorbent hydrogels by minimizing the consumption of chemicals or improving the degradability of disposed hydrogels. In this context, recent innovations about the cellulose-based hydrogels have move toward the implementation of an environmentally sustainable production process [98] as well as utilization of the nontoxic cross-linking agents during the process [72].

7.2.3 Water Treatments

Rapid industry developments had caused a series of severe problems to the surroundings and the environment, such as water contamination. The release of wastewater that consists of heavy metal ions into the local waterway or environment can be harmful to plants, humans, and animals. Pollution resulted from heavy metals has been accorded more attention due to the increase in awareness regarding the hazardous effects of heavy metal ions in the environment. A number of technologies have been established for water treatments, which mainly include chemical oxidation, adsorption, pressurized membrane-based separation, etc. However, several disadvantages such as high energy consumption and the pollution caused by

traditional materials have been reported. Therefore, research-scholars have shifted their attention to the cellulose-based superabsorbent hydrogels.

Zhou and coworkers [99] prepared a novel magnetic hydrogel bead in order to remove Pb^{2+} from the polluted streams. The authors blended the chitosan with carboxylated cellulose nanofibrils, amine-functionalized magnetite nanoparticles, and poly(vinyl alcohol) by using instantaneous gelation method. This novel magnetic hydrogel beads can be used to absorb Pb^{2+} metal ion in sewage effectively, which are mainly attributed to the various carboxylate groups on the carboxylated cellulose nanofibrils as well as the abundant amino and hydroxyl groups on the chitosan [69]. Tripathy et al. [100] examined the metal ion sorption behavior of cellulose-based superabsorbent hydrogels (sodium carboxymethylcellulose-g-*N*-vinylformamide) to the selected metal ions including Hg^{2+}, Pb^{2+}, Zn^{2+}, Ni^{2+}, and Cu^{2+}. They found that the values of the percent ion uptake were 8.7, 9.0, 9.8, 11.5, and 13.8 at the maximum values, respectively. On the other hand, a study reported by Kamel et al. [101] proved that the cyanoethyl cellulose-based superabsorbent hydrogels were capable of the adsorption of copper (II) ions from aqueous solution effectively. The authors reckoned that metal ion removal mainly depends on the protonation and deprotonation properties of its acidic and basic groups, specifically pH value. A similar finding has been reported by Abdel-Aal's group [102] in which the metal ion absorption capacities increased with the increase of pH values. They prepared the maize starch-acrylic acid hydrogels by radiation grafting technique, and the obtained hydrogels were used to remove the heavy metal ions (Fe^{3+}, Cr^{3+}, Pb^{2+}, and Cd^{2+}) from wastewater. Hashem et al. [103] reported three types of hydrogels which were prepared via graft polymerization of acrylonitrile into maize starch and ceric ammonium nitrate which were used as the initiator. The study has proven that the prepared hydrogels could be used for the removal of Hg(II) ions from aqueous solutions with the maximum adsorption capacity of 1250 mg/g. The adsorption data agreed with the Freundlich and Langmuir isotherms.

Apart from the metal ion pollution, increasing oil contamination and oil spills from the industrial wastewater have become a new source of water pollution. In order to be cost-effective and an energy-efficient oil separation, Rohrbach's group [104] has fabricated the nanofibrillated cellulose-based superabsorbent hydrogel as the filter for water/oil separation. The fabricated filter possesses oleophobic and hydrophilic properties, resulting in an increase in filter life and reduced negative impact toward the environment while showing the efficiency of more than 99% under gravitational force. Basically, cellulose nanofibril-based aerogels have been of great interest as absorbent materials owing to their biodegradability, high absorption capacity, large surface area, and low density. In addition, the hydrophobic aerogels have been designed to contribute excellent absorption tendency for various oil from water [105].

7.2.4 Biomedical (Controlled Drug Delivery, Scaffolds for Regenerative Medicine, Wound Dressings)

In 1960, poly-2-hydroxyethylmethacrylate was used as a synthetic biocompatible hydrogel for the application of contact lens. Wichterle and Lim reported the

cross-linked poly-2-hydroxy-ethylmethacrylate hydrogel using ethylene glycol dimethacrylate as a starting material [106]. The hard contact lenses are primarily made up of hydrophobic materials such as poly(hexa-fluoroisopropyl methacrylate) or poly(methyl methacrylate), while soft lenses are based on hydrogels [107]. Usually, contact lenses are classified as soft or hard, according to their elasticity. Albeit the hard lenses are longer lasting compared with soft lenses, they tend to be poorly accepted by the users and require a lengthier adaptation period. Many efforts are made to obtain lenses with good oxygen permeability. For this purpose, several hydrophilic monomers are proposed including methacryloylamino-4-t-butyl-2-hydroxycyclohexane, 4-t-butyl,2-hydroxycyclohexyl methacrylate, and 4-t-butyl,2-hydroxycyclopentyl methacrylate with hydroxyethyl methacrylate and *N*-vinyl-2-pyrrolidone. After that, a significant progress has been accomplished, and a diverse range of polymers have been used for the fabrication and synthesis of hydrogels for various applications.

The cellulose superabsorbent hydrogels have gained noticeable interests in the application of controlled drug delivery system. This is due to their remarkable characteristics such as versatility and flexibility in fabrication; high tunability in the chemical, physical, and biological properties; variety in composition; excellent biocompatibility; and high moldability in shape [108]. One of the most notable characteristics of hydrogels is the highly porous structure, which permits a depot maintaining a high local concentration of an active pharmaceutical ingredient or drug at the targeted tissues over a long period, ranging from hours to weeks [109]. The transportation capability of high porosity of hydrophilic/hydrophobic molecules is important for a hydrogel-based drug delivery system. The drug diffusion and release behavior via the polymer network can easily be adjusted by manipulating the cross-linking density in the gel matrix and monitoring the porosity (i.e., mesh size) of hydrogels [109]. Also, the porous structure allows the drugs to be loaded and then released continuously. So far, the drug can be loaded into a hydrogel followed by releasing to the targeted place through several mechanisms: swelling controlled, chemically controlled, diffusion controlled, and environmentally responsive release. He et al. [41] fabricated the multilayered tubular and onion-like cellulose-based superabsorbent hydrogels for the first time. Their results indicated that the multilayered superabsorbent hydrogels are important and have a great potential application in the biomedical field due to its non-cytotoxicity, good architectural stability, good biocompatibility, and solvent resistance against acetone, ethanol, dimethylacetamide (DMAc), and sodium hydroxide aqueous solution.

It is known that the drug release rate is highly dependent on the network parameters (i.e., mesh size and degree of cross-linking) as well as the water content of the swollen hydrogel [110]. In the typical matrix systems, the drug is dissolved or dispersed uniformly throughout the 3D structure of the hydrogel. The drug is released through the macromolecular pores or mesh, and the initial release rate of drug is proportional to the square root of time. Depending on the structure of the hydrogels used, the chain dissolution takes place along with the swelling process due to the physical nature of the hydrogel network; thus, the release of drug results from the complex combination of diffusion, swelling, and erosion mechanisms. When

using hydrogels to modulate the bioactive molecules and drug release, the loading of the drug is performed either during network formation or after cross-linking [111]. Moreover, the bioactive molecule can be physically or covalently linked to the polymer network and further tune the release rate. It is important to note that the cross-linking reaction has to be conducted under mild conditions in order to prevent the denaturate of loaded bioactive molecule. Although hydrogel formulations for transdermal and oral delivery can be non-degradable, the direct delivery of drugs to different body interest sites requires the hydrogel biodegradation. This is to avoid foreign body reaction, and further surgical removal is necessary [45]. At present, injectable hydrogel formulations are mostly appealing and still under investigation. Recently, a new and novel injectable cellulose nanocrystal-reinforced superabsorbent hydrogel has been developed by Yang's group [112] which could maintain their original shape for more than 60 days when immersed in 10 mM phosphate buffered saline or purified water and exhibits the excellent storage modulus. These properties make nanocellulose-reinforced injectable hydrogels a high potential interest for various biomedical applications such as tissue engineering matrices or drug delivery vehicles.

In the last decade, the use of excellent biocompatibility cellulose hydrogel and its derivatives as biomaterials for the design of tissue engineering scaffolds has received increasing attention. Regenerative medicine is an interdisciplinary research which deals with the induced regeneration of organs and tissues in vivo, by means of a scaffolding template or material that support and guide the cells during the synthesis of new tissues. In other words, it involves the replacement or improvement of specific organs or tissues using engineered materials and synthetic strategies. Basically, the superabsorbent hydrogels can be altered by using linker molecules that enable covalent or non-covalent molecular interactions between the hydrogel matrix and its surroundings in order to enhance the mechanical performance and tissue-/cell-adhesive properties [3].

For an ideal tissue regeneration, the generated scaffold has to be biodegradable with a reasonable biodegradation rate that matches with the biological process of the body. Practically, a slow degradation process is often favored to minimize the risk of premature resorption of the scaffold. Due to the bio-durability of cellulose, it is a suitable candidate for the design of tissue engineering scaffolds. However, it is known that a too slow degradation or a bio-durable material may cause the undesired biological responses in the long term, such as foreign body reaction, which limits the applications of cellulose in regenerative medicine. In fact, several studies [113, 114] have been conducted to prove the potential application of cellulose-based hydrogels for inducing the regeneration neural tissues, cartilage, and bone. A final remark about the development of regenerative medicine concerns the important role played by the scaffold porosity, which enhances the infiltration, attachment, and survival of cells within the scaffold. Owing to its nano-dimensional mesh structure [110], the superabsorbent hydrogels are usually employed to the small tissue defects while failing in larger implants. Several novel techniques for producing porous hydrogels had been summarized in several review papers [3, 45] and might be of great value in improving the regenerative potential of cellulose-based superabsorbent hydrogels.

In addition, there has been considerable interest in using cross-linked carboxymethyl cellulose (CMC) as tablet disintegrants. In order to achieve this, the cellulose superabsorbent hydrogels in powder form is mixed well with other excipients and thus is compressed to a tablet. Sadly, the cellulose-based superabsorbent hydrogel tablets may get soften at high-humidity condition, and thus, it may have an instability concern to the moisture-sensitive drugs [115]. Tissue engineering is the latest application of hydrogels which is mainly served for three purposes including as delivery vehicles for bioactive substances (for encapsulation of secretory cells and promotion of angiogenesis), as space-filling agents (to prevent adhesion, employed for bulking and as biological glue), and as three-dimensional structures that organize cells and present stimuli in order to ensure the development of a required tissue in the body (i.e., smooth muscle, bone, and cartilage) [111].

Superabsorbent hydrogels are widely applied in the wound treatment. During the wound healing, several processes including inflammation, autolytic debridement, granulation tissue formation, and reepithelialization are normally involved. Large wounds result in high risk of infection as well as loss of large amounts of fluids. Therefore, suitable wound dressings are designed to promote healing while protecting the wound from further infection. For an ideal wound management product, it should have numerous properties such as being able to absorb excess toxins and exudate, preserve the wound from external infection, prevent excess heat at the wound, maintain good moisture between the dressing and wound, have good permeability to gases, be easy to remove without further trauma to the original wound, and be supplied completely sterile [116]. It is known that a moist environment encourages rapid healing; therefore, the hydrogels in the form of sheets or amorphous state are optimal candidates for the development of wound dressings [117]. Basically, amorphous hydrogels are physically cross-linked, and their viscosity will be decreased when absorbing the physiological fluids. Amorphous-state hydrogels are generally reapplied daily, while the sheet structure hydrogels are usually changed 2–3 times weekly [3]. The hydrogels may be packaged in foil packets or in tubes and can reinforce with a polymeric mesh or gauze for the ease of removal and to prevent gel liquefaction. The advanced dressings are aimed to keep the moist environment at the applied site, allowing the fluids to remain close to the wound rather than spread to the healthy, unaffected skin areas [118]. The significance of the moist condition around the wound as a factor accelerating the healing process was first observed in 1962 by Winter [119] but only has received much attention recently.

Besides that, hydrogels are used as moist dressings, debriding agents, and components of pastes for wound care. Yet, they do not prerequisite wound fluids to convert into gels and, thus, are suitable for dry wounds [120]. It is worth mentioning that the superabsorbent hydrogels are able to provide non-adherent dressings which can be easily detached from the wound bed without further hurt. A further advantage of hydrogel is the transparency properties as the user can easily monitor the condition of wound healing. In recent year, the antimicrobial agents, such as silver ions, have been included in the formulation of hydrogel dressing production, as shown in Table 8. Bacterial cellulose has been extensively

Table 8 Commercially available hydrogel for application of wound dressings [45]

Hydrogel wound dressing	Producer	Composition
IntraSite™ Gel	Smith & Nephew	Propylene glycol, water, NaCMC
Aquacel Ag™	ConvaTec	NaCMC, silver ions (1.2%)
GranuGel™	ConvaTec	Water, NaCMC, propylene glycol, pectin
Purilon Gel™	ColoPlast	Water, calcium alginate, CMC
Silvercel™	Johnson & Johnson	Calcium alginate, silver ions (8%), CMC

investigated for wound healing due to its high purity and excellent water retention capacity, and a series of bacterial cellulose-based wound dressing are currently marketed [121].

8 Formation Mechanism of Cellulose-Based Hydrogels

In general, there are three main types of hydrogel-forming mechanisms: chemical cross-linking, ionotropic cross-linking, and complex coacervate formation. The mechanism for the formation of hydrogels (gelation behavior) has a direct and significant impact on the methods used to fabricate the hydrogel component for tissue engineering. Certain gel-forming processes resulted in the rapid prototyping fabrication process, while the slower fabrication techniques (i.e., porogen leaching) are suitable for robust hydrogels, which normally require more time to develop [122]. All hydrogels possess physical attraction between macromers due to the presence of hydrogen bonding and entanglements among one another [20]. Unfortunately, these physical interactions are strong enough only for the formation of a weak gel but not strong enough for tissue engineering applications or layer-upon-layer fabrication. Therefore, a hydrogel is usually intended for tissue engineering applications which must be strengthened through additional chemical cross-linking or electrostatic interactions.

In the current era, chemical cross-linking is the highly resourceful method for the formation of hydrogels having an excellent mechanical strength. Cross-linking is responsible for the three-dimensional network structures of hydrogels and their physical properties (i.e., swelling and elasticity) that are attributed to the presence of chemical or physical cross-links within polymer chains. The cross-linking level of the hydrogels is also vital because the physical states of the hydrogels can be altered by changing the cross-linking level [123]. In this process, a cross-linking agent is added to a diluted hydrophilic polymer solution, and the polymer must have a suitable functionality to react with the cross-linking agent. This process is applicable for preparation of hydrogels from synthetic and natural hydrophilic polymers [124].

Ionotropic hydrogels are formed from the electrostatic interactions between polycations and anions or polyanions and cations. For instance, chitosan is a polycationic polymer comprised of glucosamine residues, which form a firm ionotropic hydrogel upon addition of phosphate ions and which are positively charged above its isoelectric point [11]. Another example is alginate, a polyanionic

polymer containing glucuronic and mannuronic residues, which will form a firm ionotropic hydrogel with calcium ions [125]. Usually, these hydrogels are able to form a firm hydrogel upon cooling; therefore, it is particularly useful for use in rapid prototyping fabrication techniques or for in situ tissue engineering [126]. Normally, ionic cross-links are beneficial for biomedical applications due to its self-repair properties. Thus, it is proposed to be used as cartilage tissue scaffolds which consist of epoxy amine polymers and gellan gum (a water-soluble anionic polysaccharide) [127].

Complex coacervate hydrogels (as referred to polyelectrolyte complexes or polyion complexes) are formed upon mixing of a polycation and a polyanion with one another (i.e., poly(L-lysine) and alginate) or with an amphoteric polymer (i.e., gelatin and chondroitin sulfate) [20, 128]. This approach is based on the principle that the opposite charges of the polymers stick together to form either soluble or insoluble complexes, depending on the pH and concentration of the solutions [38]. Hydrogels can be produced by a variety of cross-linking methods as well as agents. However, most of the cross-linking agents are toxic and must be eliminated from the hydrogel before contact with the body or cells.

9 Conclusion

Considering the desirable features of hydrogels in terms of biocompatibility, biodegradability, high water content, controllable swelling behavior, low cost, hydrophilicity, and non-toxicity characteristics, cellulose-based superabsorbent hydrogels that are made from natural biomass resources are drawing attention to both industrialist and academicians. These types of novel hydrogels are potentially used for a variety of industrial applications such as drug delivery system, agriculture, tissue engineering, water engineering, hygiene products, wound dressing, and more. In this chapter, we had summarized several polymerization reaction systems that were widely used for the superabsorbent hydrogel production. In addition, stimulate-responsive cellulose-based hydrogels established a new generation of green materials to be applied in several fields, such as pharmaceutical and medical systems. According to different applications, these materials are able to respond to various internal and external stimuli and are sensitive to the changes of temperature, pH, ionic strength, and solvent system. Undoubtedly, superabsorbent hydrogels derived from cellulose and cellulose derivatives offer abundance of promising opportunities in various industries' usage.

10 Outlook/Future Scope

This chapter discusses the current progress of cellulose-based superabsorbent hydrogels from different aspects. Generally, cellulose-based superabsorbent hydrogels possess several favorable properties such as biocompatibility, biodegradability, hydrophilicity, transparency, low cost, and non-toxicity. Therefore, these

bio-based materials offer a wide variety and diverse range of applications for agriculture and horticulture, water treatments, personal health care, and biomedical industries. Nevertheless, some of the novel applications need to be explored, such as electronics, catalysis, capacitors, dye-sensitized solar cells, plugging agent, biosensor, and fire control. Up to date, the established conventional hydrogel-based product could not meet the requirements of the present day and thus the future development on superabsorbent hydrogels by emerging natural biomass resources (cellulose or cellulose derivatives) with the intention of achieving the demands for different product requirements. From the economic and application point of view, the performance of superabsorbent hydrogels (e.g., distinctive mechanical strength, antimildew properties, swelling capability, and electrochemical properties) can be further improved in order to expand to more industrial field. As a result, intense research on the production of cellulose-based superabsorbent hydrogels has to be conducted continuously. It is worth mentioning that cellulose fibers are low cost and is an environmentally friendly material, which is the suitable alternative of petroleum-based materials. Up to date, many hydrogel-based drug delivery devices and scaffolds have been designed, studied, and patented; however, not much of the products are able to reach commercialization stage. On the other hand, commercial hydrogel products for tissue engineering and drug delivery are still limited. It is believed that the limited commercial products with hydrogels in these areas are due to high production costs. Furthermore, advanced technologies need to be further developed in order to produce superabsorbent hydrogels with intrinsic and unique properties. Most important is an in-depth study on the reaction mechanism, and swelling kinetics of superabsorbent hydrogels originated from interdisciplinary angles is needed for deeper investigation.

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Benefits of Renewable Hydrogels over Acrylate- and Acrylamide-Based Hydrogels

7

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Contents

Abstract

In recent years, renewable/biodegradable polymer-based hydrogels have attracted great interest in the field of hydrogel research and development. The reasons of this interest are their applications in versatile fields including personal care products; drug delivery systems; wound healing; tissue engineering; industrial, pharmaceutical, and biomedical, agricultures; water treatments; food packaging; etc. Other important reasons are the problems caused by synthetic sources to the environment. Therefore, it is our demand to develop natural materials that can be biocompatible and biodegradable with the environment, and important efforts are focused on finding alternatives to replace the synthetic one. Furthermore,

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renewable hydrogels display unique properties such as biodegradability, biocompatibility, stimuli-responsive characteristics and biological functions. Natural hydrogels are often based on polysaccharide or protein chains. Due to the hydrophilic structure of polysaccharides, they have a good property to form hydrogel. There are various polysaccharides like starch, cellulose, sodium alginate, chitosan, guar gum, carrageenan, etc. that have been focused and used for the preparation of environmental friendly hydrogels. Among them, cellulose and its derivatives revealed distinctive benefits because they are the most abundant natural polysaccharide having low cost and better biodegradability and biocompatibility. Protein chains, which form natural hydrogels, are collagen, silk, keratin, elastin, resilin, and gelatin. On the other hand, many synthetic polymers/copolymers also form hydrogel like poly(vinyl alcohol), polyacrylamide, poly(ethylene oxide), poly(ethylene glycol), etc. Synthetic polymer-based hydrogels have one benefit of chemical strength than natural counterpart due to the slower degradation rate of the hydrolyzable moieties. However, biorenewable polymers usually present higher biocompatibility compared to synthetic polymers, as they undergo enzyme-controlled biodegradation by human enzymes (e.g., lysozyme) and produce biocompatible by-products. This chapter focused on the advantages of biorenewable hydrogels over synthetic (acrylate- and acrylamide-based) hydrogels.

Keywords
Renewable hydrogels · Synthetic hydrogels · Biopolymer · Polysaccharide · Protein chains

1 Introduction

In nature, polymers are extensively distributed, and they are derived from renewable sources and commonly termed as natural polymer [1]. These natural polymeric materials show a huge variety of chemical structures, diverse physiological functions, and other biological properties. For example, they have physiological properties like tissue; they are bioactive, degraded by naturally occurring enzymes, have less inflammatory response, etc. Consequently, hydrogels prepared from renewable sources/polymers are gaining a great interest. Hydrogels can be defined as a three-dimensional network of polymer chains (may contain inorganic/organic cross-linker), which is hydrophilic in nature and can absorb huge amounts of water or biological fluids. Hydrogels from polymer become the fast developing group of materials due to their wide range of application in different disciplines, especially pharmacy, medicine, agriculture, and environment. At the end of 1960s, Wichterle and Lim first reported about the hydrogel preparation [2], and subsequently these incredible materials emerged as an indispensable part in different fields of applications. In 1980, Lim and Sun developed hydrogels of calcium alginate microcapsules and used in cell encapsulation [3]. Again, at the end of 1980s, another important work was done by Yannas and coworkers with natural polymers [4]. They prepared

hydrogels by incorporating natural polymers (e.g., collagen and shark cartilage) and applied them for artificial burn dressings. Renewable or biodegradable hydrogels also have similarity with natural living tissue more than any other type of synthetic biomaterials. They have high water absorption capacity and soft consistency and resemble to natural tissue [5]. Their biocompatibility related to high water content of these materials. Hydrogel-forming polymers do not dissolve in aqueous solution at physiological conditions. Nevertheless, they swell substantially in water or biological fluid [6] and exhibit amazing ability (>20%) to absorb water into their network structure. Hydrogels exhibiting a phase transition behavior with changing external conditions like pH, temperature, ionic strength, and electric currents are called stimuli-responsive/smart gels [7]. Hydrogels with 3D hydrophilic networks can absorb large amounts of water as they are insoluble in water. This property attributes to their good blood compatibility and keeps a firm amount of structural integrity and elasticity [7]. Due to these types of special properties, recently hydrogels are fast emerging group of materials, achieving extensive application in the fields of personal care products; drug delivery systems; wound healing; tissue engineering; industrial, pharmaceutical, and biomedical; agricultures; water treatments; food packaging; etc. [5, 8–15].

Based on network formation hydrogels can be of three types:

(a) Physical hydrogels – usually formed by electrostatic interactions between oppositely charged biopolymers.
(b) Chemical hydrogels – can be prepared by applying inorganic/organic cross-linkers to covalently bridge biopolymers at reactive sites.
(c) Interpenetrating polymer networks (IPN) – these are physical entanglements of polymers which form a distinct network as shown in Figs. 1 and 2.

Natural or synthetic polymers can be used to prepare physical and chemical hydrogels. The network formation of molecular association occurred, even though they form mixed organization of free domains (Fig. 1) [16]. Weak interaction forces like hydrophobic interactions, ionic interactions, or hydrogen bonding are responsible for the formation of physical hydrogels [9]. It is also called reversible or pseudo gels because it can be degraded or disintegrated in water and easily melts on heating. On the other hand, in chemical hydrogels network formation occurred by covalent bond formation, and therefore it is also called irreversible or permanent gels (Fig. 1) [17]. They cannot be dissolved or disintegrated in water or aqueous solutions. Another type of hydrogel, "IPN," can be defined as a physical blend of cross-linked polymers, where a minimum of one polymer needed to be synthesized and/or cross-linked within the instantaneous presence of the other. Without breaking the chemical bonds, these blends cannot be separated [18, 19]. IPN hydrogels can be classified again in three types according to the method of preparation such as (i) simultaneous IPN [18] (Fig. 2a), (ii) sequential IPN (Fig. 2b), and (iii) semi-IPN [18, 19]. If a linear polymer (synthetic or biopolymer) is entrapped in a matrix and form a semi-IPN hydrogel, then a fully IPN would be prepared later by a

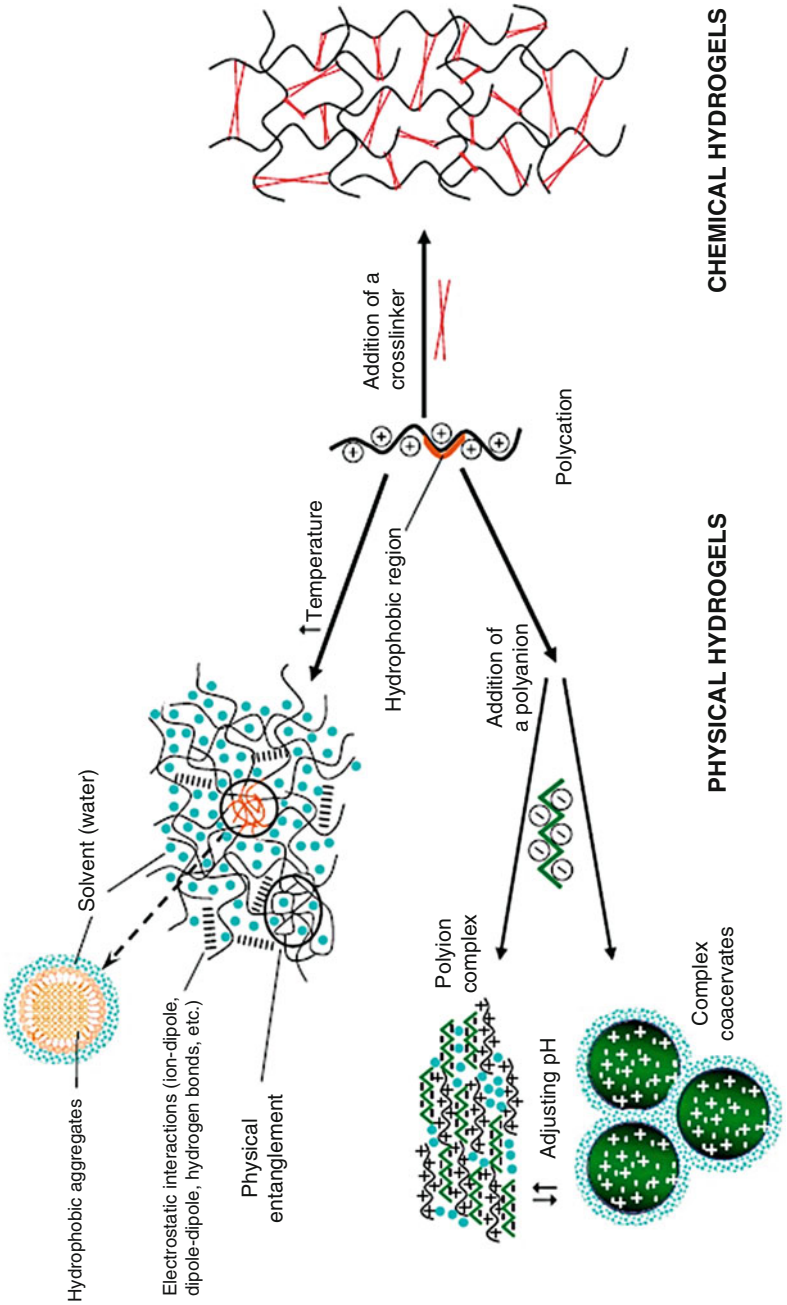

Fig. 1 Common mechanism for the formation of physical and chemical hydrogels. (Reprinted with permission from Ref. [15]. Copyright © 2017, Elsevier)

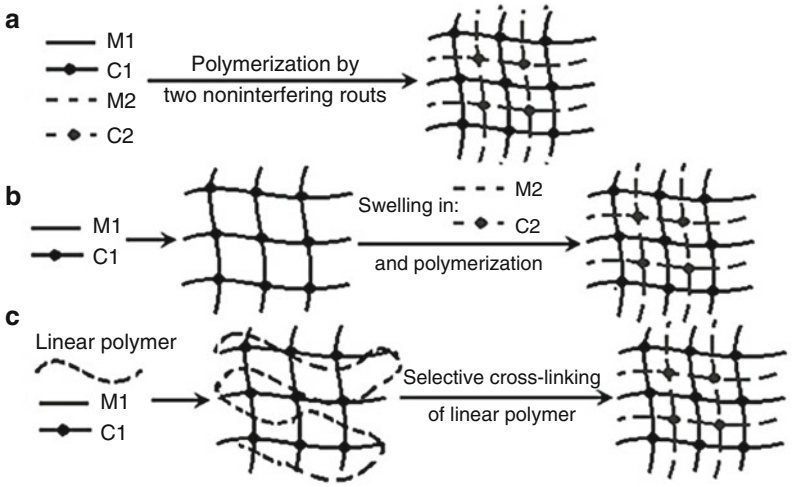

Fig. 2 Common mechanism for the formation of physical and chemical hydrogels. (Reprinted with permission from Ref. [15]. Copyright © 2017, Elsevier)

selective cross-linking of the linear polymer chains [20, 21] (Fig. 2c). Again, based on the preparation methods, this 3D structure of hydrogels could be divided into homopolymeric and copolymeric. These copolymeric thermoplastic biodegradable hydrogels also have been prepared for biomedical uses like drug delivery system [22, 23]. Another special type of hydrogel name is superabsorbent hydrogels. These are also hydrophilic networks capable of absorbing large quantity of water, have high swelling property, and can retain aqueous solutions up to hundreds of times their own weight [24–26].

As it was mentioned earlier, biorenewable hydrogels have many benefits over synthetic hydrogels and there are many reasons. Another important reason is the problems created by synthetic sources to the environment [27]. Hence, scientists are trying to develop natural materials to replace the synthetic one that can be biocompatible and biodegradable, which will not be harmful to the environment [28]. Among the different types hydrogel, renewable hydrogels show distinctive properties like biocompatibility, biodegradability, stimuli-responsive features, and biological functions [29, 30]. Natural or renewable hydrogels are usually based on polysaccharides or proteins. Polysaccharides can form hydrogel easily because of their hydrophilic chemical structure. There are many types of polysaccharides, which can be applied to prepare environmental friendly hydrogels such as cellulose, starch, chitosan, sodium alginate, guar gum, carrageenan [31–33], etc. Among them, cellulose and its derivatives revealed distinctive benefits because they are the most abundant natural polysaccharide having low cost and better biodegradability and biocompatibility [8, 34]. Proteins are another source of renewable hydrogels, prepared from natural extracellular matrix composed of isolated or enriched proteins. These hydrogels are favorable candidates as smart biomaterials due to their inherent

and controllable properties. They have excellent properties to be used in biomedical applications such as natural cell binding, cell degradable, and growth factor-binding sequences. Some of the examples of protein chains forming natural hydrogels are collagen, silk, keratin, elastin, resilin, and gelatin [35, 36]. On the other hand, various synthetic polymers/copolymers also form hydrogel such as polyacrylamide, poly(vinyl alcohol), poly(ethylene glycol), poly(ethylene oxide), etc. Compensating the limitations of synthetic polymer-based hydrogels, they have one advantage of chemical strength than natural one due to the slower degradation rate of the hydrolyzable moieties [37–39]. Conversely, biorenewable/natural polymers generally show higher biocompatibility, if we compare with synthetic polymers. Natural polymers also undergo enzyme-controlled biodegradation by human enzymes (e.g., lysozyme) and produce biocompatible by-products [40].

This chapter will be focused on details about the advantages of biorenewable hydrogels over synthetic hydrogels especially acrylate- and acrylamide-based hydrogels. Moreover, it will discuss about the renewable or biorenewable polymer-based hydrogels, their sources, preparation methods, types, properties, and applications. It will cover the information about newly developed biorenewable hydrogels. Furthermore, the advantages of biorenewable hydrogels over synthetic hydrogels especially acrylate- and acrylamide-based hydrogels will be discussed. Finally, future scope of these types of hydrogels is also described.

2 Renewable Hydrogels from Biopolymers

Renewable hydrogels, obtained from biopolymers, are the most widespread and effective materials because of their safety, biocompatibility, hydrophilicity, biodegradability, and wide applicability [41–43]. The demand of biopolymeric materials is increasing due to the problems caused by the use of different types of synthetic sources. Biopolymers are polymers produced from living organisms and are always renewable, because they are made from plant materials that can be grown indefinitely. Biopolymer contains monomeric units that are covalently bonded to form larger structures. There are three main classes of biopolymers: polynucleotides (RNA and DNA), polypeptides, and polysaccharides [44, 45]. Biodegradable natural polymers are mainly based on renewable sources such as starch, alginate, gelatin, chitosan, cellulose, etc. and can be produced naturally or synthesized from renewable sources. These biodegradable polymers have wide applications in a variety of fields such as agriculture, food industry, wastewater treatment, medicine, cosmetics, tissue engineering, drug delivery and wound healing, packaging industry, removal of heavy metals, and so on. Synthetic polymers including poly(vinyl alcohol), polyacrylamide, poly(ethylene oxide), and poly(ethylene glycol) have also been used for the formation of hydrogels [46]. But natural polymers usually show higher biodegradability and biocompatibility compared to synthetic polymers, as they undergo enzyme-controlled biodegradation by human enzymes like lysozyme that produces biocompatible by-products [47]. In the following sections, details about biorenewable hydrogels (polysaccharide- and protein-based) will be discussed.

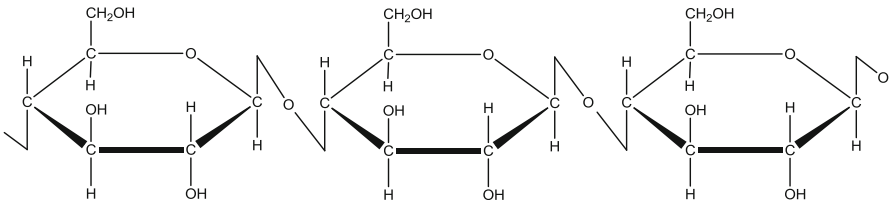

Fig. 3 Structure of cellulose

2.1 Polysaccharide-Based Hydrogels

Polysaccharides have hydrophilic structure which is a favorable property for the preparation of renewable hydrogels [48]. The ever-increasing interest to utilize renewable polysaccharide-based hydrogels as biomaterials has gained increased attention in many disciplines including biomedicine, bioengineering, pharmacy, chemistry, and materials science. Some examples of polysaccharide-based hydrogels are hydrogels made of alginate, cellulose, chitosan, starch, and guar gum. Preparation reactions for polysaccharide-based hydrogels can be classified into two main groups: (1) graft copolymerization of vinyl monomers on polysaccharide in the presence of a cross-linker and (2) direct cross-linking of polysaccharide [49]. Various kinds of polysaccharide-based hydrogels are discussed in the following sections.

2.1.1 Cellulose

Cellulose is the most abundant biopolymer on earth, thus having great potential in hydrogel preparation. From a chemical point of view, cellulose is a polydispersed linear homopolymer that consists β-(1→4)glycosidic-linked D-glucose units, which gives rise to a linear syndiotactic polymer with hydroxyl groups arranged in an equatorial disposition (Fig. 3). The main source of cellulose is the main constituent of the cell walls of plants. Cellulose is traditionally used as a raw material for the production of paper, paperboard, fiberboard, textile fibers, stabilizer, thickener, gelling agent, etc. [50].

Cellulose-based hydrogels, obtained from different low-cost routes, have excellent biodegradable and biocompatible properties. Such bio-friendly behavior makes cellulose-based hydrogels appealing for smart application in a variety of fields. Cellulose-based hydrogels can be obtained from cellulosic (native cellulose and its derivatives) via cellulose dissolution and physical as well as chemical cross-linking strategies. Composite hydrogels with specific properties can be prepared by using cellulose in conjunction with natural and/or synthetic polymers. The major advantage of cellulose-based hydrogels is that they are easily modifiable and have good transport properties. In view of expanding the scope of hydrogel applications, it is important to take full advantage of the unique structure as well as physical and chemical properties of hydrogels to develop novel materials with promising new features. Several approaches were developed to prepare cellulose-based renewable hydrogels.

Hydrogels Prepared Directly from Native Cellulose

Cellulose hydrogels can be prepared from a cellulose solution through physical cross-linking due to hydroxyl groups, which can easily form hydrogen bonding linked network. The main limitation of cellulose hydrogels is the low solubility of cellulose in both water and most organic solvents due to the hydrogen-bonded structure [51]. This problem can be avoided by using new solvents such as *N*-methylmorpholine *N*-oxide (NMMO), ionic liquids (ILs), alkali/urea (or thiourea) aqueous systems, dimethylacetamide/lithium chloride (DMAc/LiCl) system, etc. to dissolve cellulose, providing great opportunities for the preparation of cellulose hydrogels. Moreover, bacterial cellulose (BC) is also a strong candidate for the fabrication of cellulose hydrogels. Nowadays cellulose hydrogels are the ideal materials for tissue engineering applications [52].

Hydrogels from Cellulose Derivatives

Water-soluble cellulose derivatives are mostly biocompatible which can be used as thickener, binding agents, emulsifiers, film formers, suspension aids, surfactants, lubricants, and stabilizers, especially as additives in food, pharmaceutical, and cosmetic industries. Selective cellulose ethers such as methyl cellulose (MC), hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose (HPMC), and carboxymethylcellulose (CMC) have been used to fabricate cellulose-based hydrogels through physical cross-linking and chemical cross-linking method.

Cellulose-Polymer Composite Hydrogels

To obtain new structural materials, blending of different polymers is an extremely attractive, inexpensive, and advantageous method [53]. Cellulose (or its derivatives) has created novel materials when blended with natural biodegradable polymers, such as chitin, chitosan, starch, alginates, and hyaluronic acid [23, 54–56] to fit the special applications, such as blending with chitosan for heavy metal removal, with starch for foods, and with alginates for tissue engineering. Poly(vinyl alcohol) (PVA) is also a good candidate for the preparation of hydrogels. Several methods are used to prepare cellulose-PVA hydrogels including chemical agents, electron beam, irradiation, or physical thermal cycling. For biomedical applications, physical cross-linking has the advantage than PVA gels cross-linked by either chemical or irradiation techniques because physical cross-linking method avoids residual amounts of toxic chemical cross-linker and shows higher mechanical strength [57].

Cellulose-Inorganic Hybrid Hydrogels

Due to potential applications in electric, optical, magnetic, and biological fields, polymeric-inorganic hybrid materials have attracted increasing attention in recent years [58]. Introduction of inorganic into cellulose hydrogel networks is an effective way to develop materials with high functionality. For instance, hydrogel made from calcium phosphate and Si-HPMC is used as an injectable and self-cross-linkable bone substitute and also developed for filling bone defects.

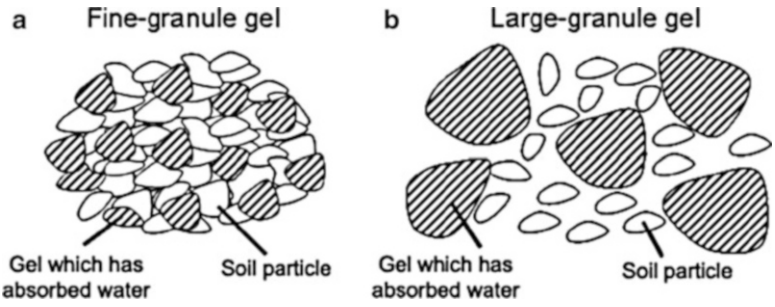

Fig. 4 Spatial distributions of hydrogels and soil particles [8]

Prospects for Applications of Cellulose-Based Hydrogels: There is an increasing interest in using cellulose-based superabsorbent hydrogels in agriculture. This is mainly due to the necessity of decreasing water consumption and boosting water resources in agriculture. Sannino and coworkers recently developed a novel class of totally biodegradable and biocompatible microporous cellulose-based superabsorbent hydrogels [59–62] which are able to absorb up to 1 L of water per gram of dry material (Fig. 4).

Due to the industrial development, the serious threat of heavy metal ions to the environment is a precise concern worldwide. Heavy metals are the most common pollutants found in wastewater and can be accumulated in the environment and living tissues. These heavy metals cause various diseases and disordering of living organisms even at a trace level [63]. Thus, it is indispensable to remove harmful heavy metals from aqueous solutions. Recently, cellulose-based renewable hydrogels have wide application for the removal of heavy metals from the aqueous solution. For example, Xiong Chen and his coworkers [64] prepared cellulose/graphene oxide hydrogel, a highly efficient bioadsorbent using NaOH/urea aqueous solution (Fig. 5). The hydrogel showed high efficient regeneration and high adsorption capacity for Cu^{2+}, Zn^{2+}, Fe^{3+}, and Pb^{2+}.

Moreover, cellulose-based hydrogels are appealing materials for a number of applications in vivo [62, 65] due to the intrinsic biocompatibility of cellulose. Also, Sannino and coworkers reported the development of cellulose-based hydrogels from the aqueous mixtures of NaCMC and HEC, which have been shown to be tempting for the production of dietary bulking agents [66, 67]. In particular, cellulose-based hydrogels obtained from nontoxic cross-linking agents are particularly attractive for this kind of application.

In another work, Sannino et al. reported that cellulose-based hydrogels cross-linked with hyaluronic acid [66] induce a good proliferation of keratinocytes, following a scratch wound model in in vitro culture. A few studies show that cellulose-based hydrogels are potentially useful for inducing the regeneration of bone, cartilage, and neural tissues [68, 69].

Tissue engineering is the most recent application of cellulose-based hydrogels. J. J. Marler et al. reported the cellulose-based hydrogels which are used as scaffolds

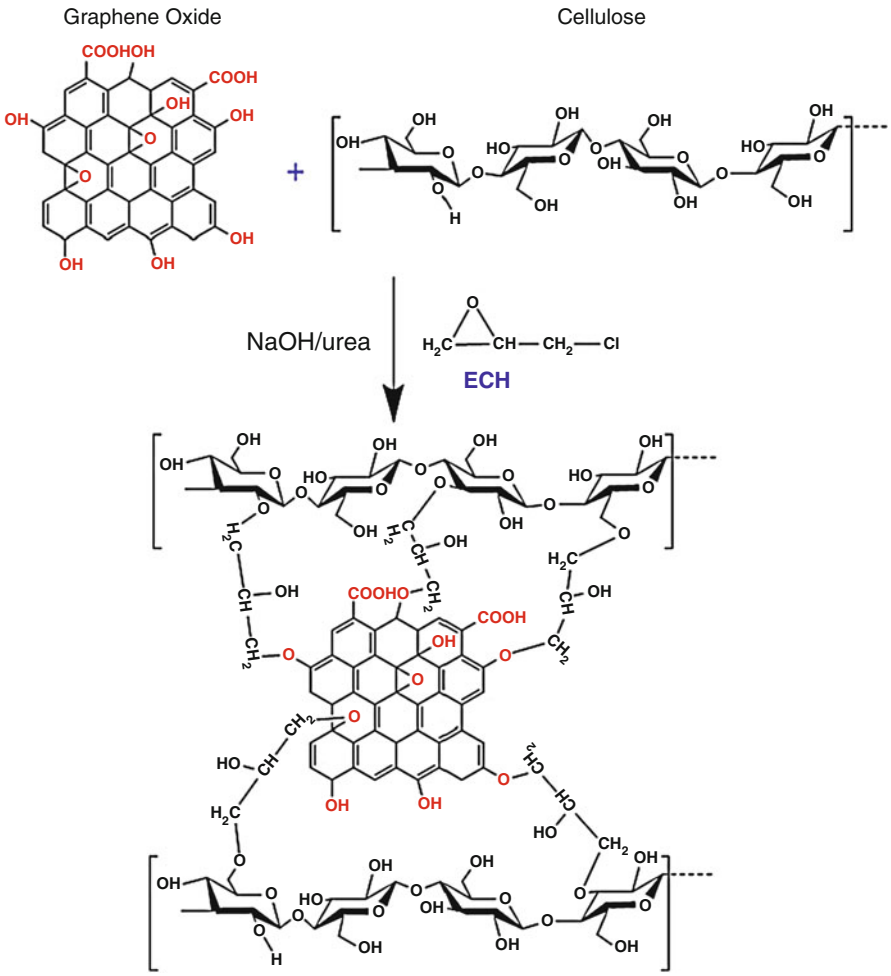

Fig. 5 Proposed mechanism for cross-linking reaction of epichlorohydrin with graphene oxide and cellulose [64]

to mimic many roles of extracellular matrixes. These scaffolds provide space and nutrients for new tissue formation and potentially control the structure and function of the engineered tissue in situ or in vitro [70]. The scaffolds also serve as a temporary, artificial, extracellular matrix in order to support the cell attachment [71, 72]. Hydrogel scaffolds are at or near clinical uses in engineering many tissues in the body including cartilage, bone, muscle, skin, fat, artery, ligament, tendon, liver, bladder, and neurons [73]. Several studies report the applicability of cellulose-based materials for culturing cells and for implantation such as bone regeneration [74, 75], hepatocyte culturing for an artificial liver [76], expansion of progenitor hematopoietic cells in culture [77], and suppression of matrix metalloprotease action in wound healing [78].

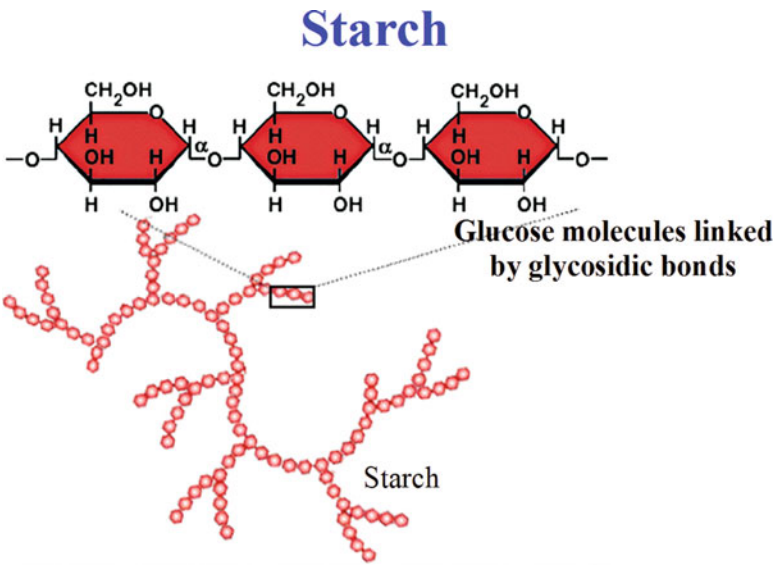

Fig. 6 Structure of starch

As we know cellulose itself has no antimicrobial activity to prevent wound infection. For that reason, to achieve antimicrobial ability, few researchers impregnated ZnO or Ag nanoparticles (NPs) into the cellulose gel system [79, 80]. Furthermore, due to their high absorbency, porous structure, rich functional groups, and relatively low crystallinity, cellulose-based hydrogels have attracted special attention for water purification through adsorption.

2.1.2 Starch

Starch is the most abundant storage polysaccharide which is composed of linear amylose and branched amylopectin (Fig. 6) and is considered the main form of stored carbohydrates in plants such as rice, potatoes, or corn [81]. Starch has gained more attention for developing renewable hydrogels by mixing with other natural or synthetic sources because of its complete biodegradability, low cost, nontoxicity, and renewability. Recently, it has been reported that starch-based polymers have better application in packaging, drug delivery systems, and tissue engineering scaffolds [82]. But the application of starch film is restricted because of its poor process ability, dimensional stability, low shear resistance, high tendency toward retrogradation, and high moisture sensitivity. This restriction has led to the necessity to associate starch with either biopolymers or synthetic polymers to preserve the biodegradability of the final product [83].

Prospects for Applications of Starch-Based Hydrogels: Recently, much attention has been given in developing starch-based renewable hydrogels [84, 85]. To retain large amounts of water, starch-based renewable hydrogels have been used for a variety of applications in the medical and pharmaceutical industries.

Viyoch et al. [86] reported the preparation of an injectable thermosensitive hydrogel for chondrocyte delivery by mixing starch and chitosan. They found that the presence of starch in the chitosan system could raise the average pore size and water absorption of the hydrogels that can be suitable for cartilage tissue engineering.

Pereira et al. [87] reported biodegradable hydrogel based on starch/cellulose acetate blends, produced by free-radical polymerization and used as biodegradable bone cements or drug delivery carrier. Fekete and coworkers [88] reported the synthesis of starch/carboxymethylcellulose superabsorbent hydrogels by gamma-irradiation technique that exhibits good swelling properties but lower sensitivity to the presence of salts or the pH of the soil. Also, Baran et al. [82] prepared starch-chitosan hydrogels by reductive alkylation cross-linking method for biomedical application.

Due to the increase in awareness about the hazardous effects of enhanced levels of heavy metal ions in the environment, pollution by heavy metals has been recently given more attention [89]. As we know, activated carbon is used as adsorbent for the removal of heavy metal ions because of its extended surface area, high adsorption capacity, and microporous structure. However, activated carbons are found to be commercially expensive, which has led to a search for cheaper adsorbents. Hashem et al. [90] reported the preparation of three types of hydrogels through the graft polymerization of acrylonitrile onto maize starch where ceric ammonium nitrate was used as the initiator. The hydrogels were used to remove Hg (II) ions from aqueous solutions. In another research, Chauhan et al. [91] prepared poly-carboxylated starch-based hydrogels as Cu^{2+} ion sorbents by the free radical initiation, and *N,N′*-methylenebisacrylamide was used as a cross-linker. The studies showed that the maximum adsorption capacity of 128.26 mg/g was obtained within 2 h at 40 °C with 7 pH and a Cu^{2+} ion concentration of 50 ppm. The possible interaction of Cu^{2+} with polycarboxylated starch-based hydrogels is shown in Fig. 7.

Superabsorbent hydrogels prepared from starch can also be utilized for electric cable production to prevent penetration of water in the cable through the junction when the outer coating of the cable is damaged. Such a special type of water-blocked telecommunication cables and water-blocked yarns was invented by Schoeck et al. [92] using a starch superabsorbent hydrogel.

2.1.3 Alginate

Alginates are binary, natural linear polysaccharide and copolymers of (1→4) linked β-D-mannuronic acid (M) and α-l-guluronic acid (G) monomers of widely different compositions and sequences (Fig. 8). The most common source of alginate is the cell wall of brown algae including *Laminaria hyperborea*, *Laminaria digitata*, *Laminaria japonica*, *Ascophyllum nodosum*, and *Macrocystis pyrifera*. For commercial purposes, alginates are extracted from seaweed [93]. Due to its biocompatibility, low toxicity, relatively low cost, and mild gelation, alginates have been widely used for many years as a potential biomaterial for many biomedical applications such as tissue engineering, wound healing, cartilage and bone regeneration, protein delivery, in vitro cell culture, antibacterial films, drug delivery [94], etc. Although alginate has a strong potential to be used in various applications, it usually lacks the desired

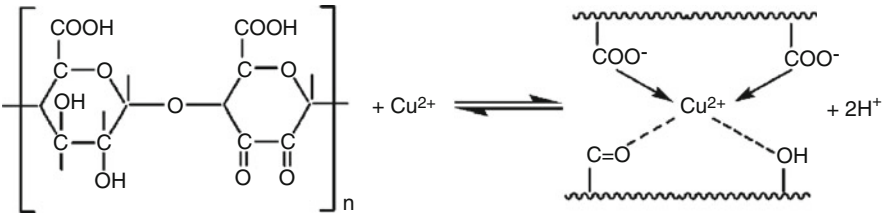

Fig. 7 Possible interactions in Cu^{2+} ion sorption. (Reprinted with permission from Ref. [91]. Copyright © 2017, American Chemical Society)

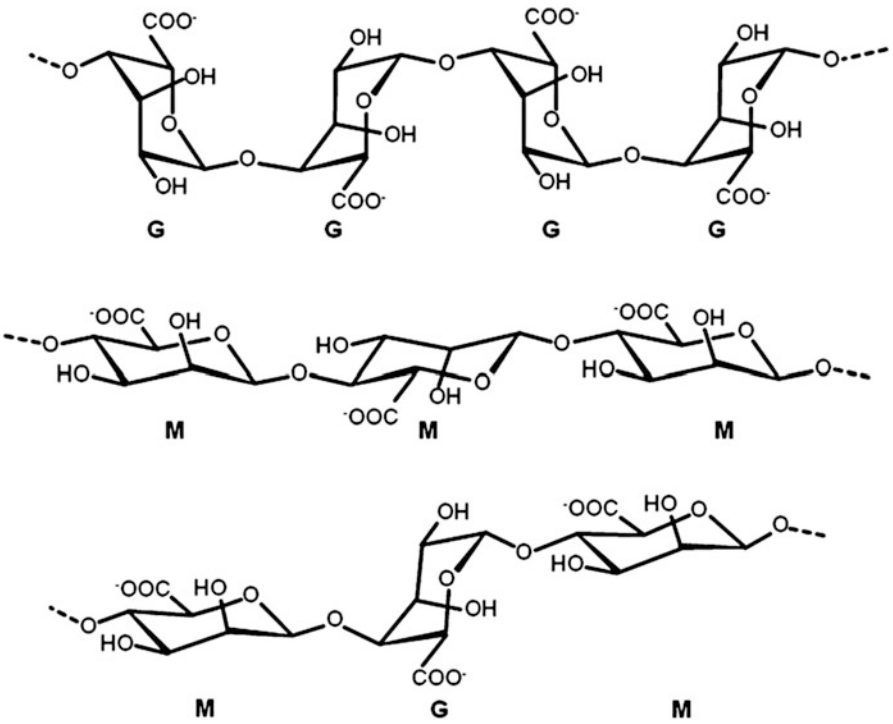

Fig. 8 Chemical structures of G-block, M-block, and alternating block in alginate. (Reprinted with permission from Ref. [95]. Copyright © 2017, Elsevier)

mechanical strength and thermal properties. For that reason, alginate is often associated with natural as well as synthetic polymers to improve the mechanical and thermal properties.

Prospects for Applications of Alginate-Based Hydrogels: Alginate-based hydrogels are considered one of the most biocompatible materials [96] and have been found applicable in several pharmaceutical and biomedical systems. For instance, they have been widely used in tissue engineering and controlled drug delivery of molecules or proteins [97, 98], cell encapsulation system [99], and

scaffolds for tissue or organ regeneration [100]. Alginate-based hydrogels are prepared by cross-linking method because cross-linked polymers have better mechanical strength than natural polymers. Several researchers developed alginate-based hydrogels using various approaches. Zhao et al. [101] reported the preparation of Janus alginate hydrogel particles with magnetic anisotropy for cell encapsulation. Navratil et al. [102] reported the preparation of alginate hydrogel by ionotropic gelation for entrapment of microbial cells for the production of fermented beverages.

Drug delivery carriers and tissue engineering systems have attracted a lot of interest during the past decades. Due to biocompatibility and low toxicity of alginate, the need for alginate-based hydrogels in tissue engineering and drug delivery is enormous and of great clinical significance. For instance, Wang et al. [103] prepared three-dimensional alginate scaffolds cross-linked with calcium ion using microfluidic method which is used for tissue engineering.

We know that sodium alginate is one of the most abundant and naturally occurring polysaccharides. Due to its biocompatibility, biodegradability, high hydrophilicity, and mechanical strength, sodium alginate has received considerable attention for its use in pharmaceutical dosage forms, particularly as a vehicle for controlled drug delivery. Kulkarni et al. [104] reported an interpenetrating hydrogel membrane using sodium alginate and poly(vinyl alcohol) for the controlled release of prazosin hydrochloride through the skin. Moreover, El-Sherbiny and Smyth developed a semi-IPN hydrogel microsphere from sodium alginate and poly(ethylene glycol)-graft-*n*-phthaloyl chitosan [105] which entrapped up to 90% of the drug with promising in vitro sustained release profiles.

Recently, a novel hydrogel system based on oxidized alginate covalently cross-linked with gelatin (ADA-GEL) has been recently developed by Detsch et al. [106] and utilized to design tissue engineering scaffolds, in which cell growth, proliferation, and migration were observed. Xu and coworkers [107] developed a hydrogel composed of alginate and chitosan, cross-linked by calcium chloride and/or sodium sulfate for colon-specific drug delivery. Bunaprasat et al. [108] reported the development of porous polycaprolactone-alginate scaffolds for cartilage tissue engineering. Furthermore, alginate-cellulose hydrogels that are prepared by solvent casting method have found applications in biomedical field especially cell proliferation and tissue generation.

Alginate-based wound dressings such as hydrogels, sponges, etc. are promising substrates for wound healing applications. Alginate/aloe vera hydrogel films prepared by solvent casting method were reported by Pereira et al. [109] for wound healing applications (Figs. 9 and 10). Balakrishnan et al. showed that an in situ-forming hydrogel wound dressing can be prepared from gelatin and oxidized alginate in the presence of small concentrations of borax [110].

2.1.4 Chitosan

Chitosan is a unique bio-based polymer that is an important derivative of chitin (found in the skeleton of crustaceans, such as crab, shrimp, lobster, etc.). It is obtained by partial deacetylation of chitin using a chemical method or by enzymatic hydrolysis [111] (Fig. 11). It is the second most abundant natural polysaccharide next to cellulose and composed of (1→4)-2-acetamido-2-deoxy-β-D-glucan

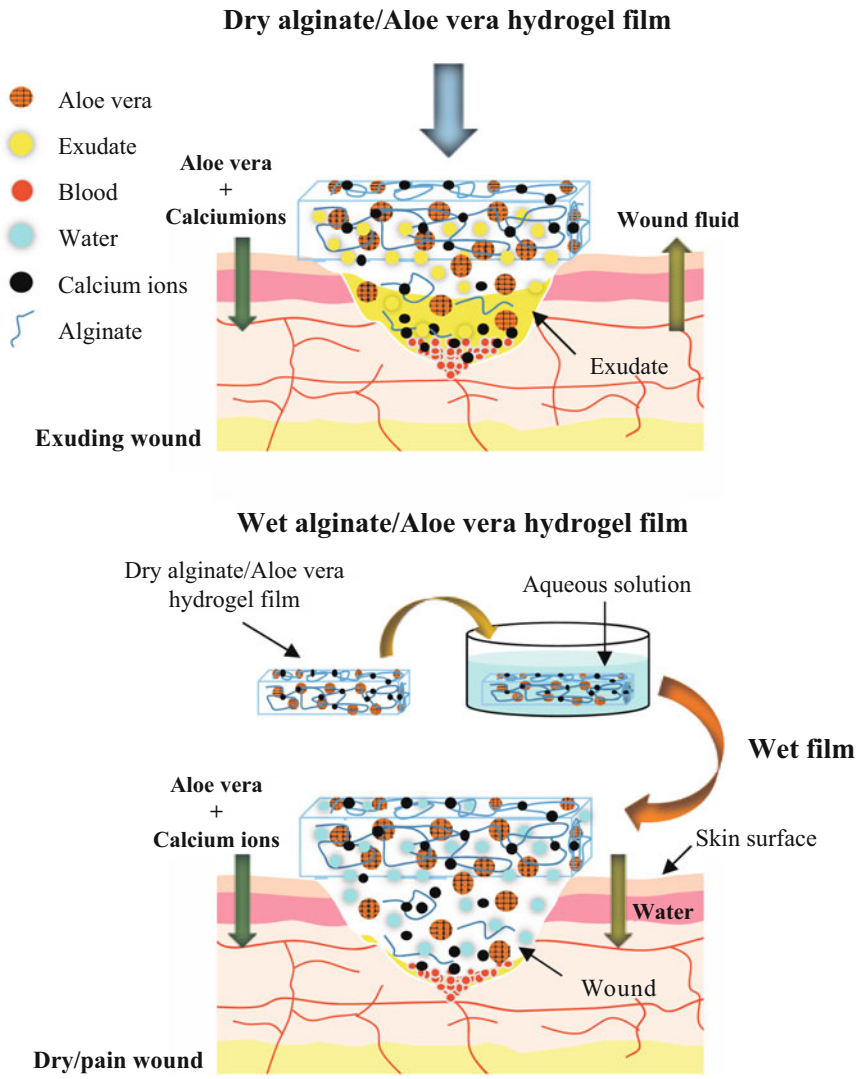

Fig. 9 Application of the alginate/aloe vera hydrogel films into exuding and dry wounds. (Reprinted with permission from Ref. [109]. Copyright © 2017, Elsevier)

(N-acetyl D-glucosamine) and (1→4)-2-amino-2-deoxy-β-D-glucan (D-glucosamine) units [112]. The high availability of chitosan and its biocompatibility and biodegradability have enhanced interest in its use as a hydrogel with potential applications in tissue engineering, biosensors, drug delivery and wound healing, wastewater treatment, removal of heavy metals, and so on [113, 114]. Chitosan has been combined with a variety of natural as well as synthetic polymers to form hydrogels which have potential applications in the fields mentioned above.

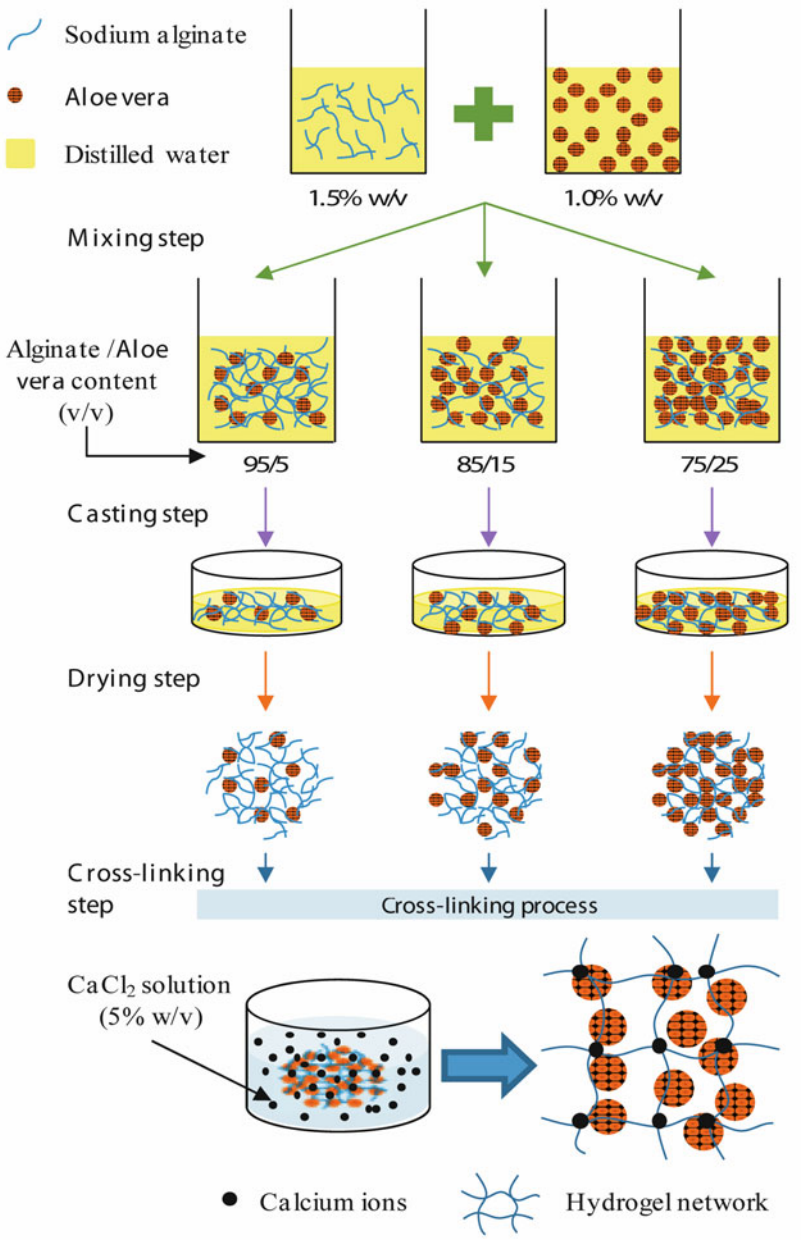

Fig. 10 Production of alginate/aloe vera hydrogel films. (Reprinted with permission from Ref. [109]. Copyright © 2017, Elsevier)

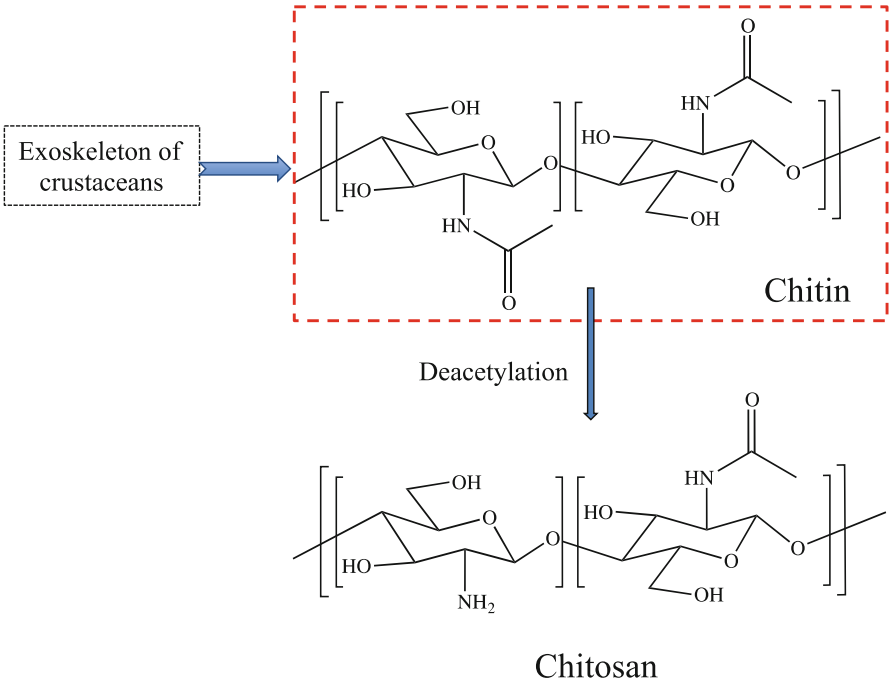

Fig. 11 Chitin is extracted from crab shell from which chitosan is made by deacetylation

Prospects for Applications of Chitosan-Based Hydrogels: Hydrogel based on chitosan and its chemically modified forms are investigated for the delivery of drug to specific sites of the body such as the oral cavity, stomach, small intestine, and colon. Chitosan has cationic nature due to the presence of amine group and therefore can adhere to negatively charged biological surfaces as a bioadhesive material that provides localized drug delivery [115]. Due to its biocompatible and biodegradable property with a structure that could be modified easily, chitosan has been used as drug carrier for different routes of administration.

A novel pH-sensitive hydrogel bead composed of N-succinyl-chitosan and alginate was developed by Dai and coworkers [116]. Chang et al. [117] reported amoxicillin-loaded pH-sensitive hydrogels composed of chitosan and poly (g-glutamic acid) for the treatment of *Helicobacter pylori* infection in the peptic ulcer disease. Interpenetrating polymer networks (IPN) of chitosan and poly(ethylene oxide) have also been developed for the treatment of *Helicobacter pylori* [118].

The high water absorption and mucoadhesive potential of chitosan facilitate its use in nasal drug delivery application. For instance, Nazar et al. [119] reported the synthesis of N-trimethyl chitosan chloride and formulated it into a hydrogel with poly(ethylene glycol) and β-glycerophosphate for nasal drug delivery. Moreover, a thermosensitive in situ gel system was prepared by mixing chitosan and poly(vinyl alcohol) for the nasal delivery of insulin [120]. In another study, Wu et al. [121]

prepared thermosensitive hydrogel by simply mixing quaternized chitosan and poly(ethylene glycol) with a small amount of a- and β-glycerophosphate for nasal drug delivery.

Chitosan in topical form is used for wound healing. The major use of chitosan hydrogels for wound healing is using these systems as wound dressing and hemostatic agent to promote the process of wound healing. A series of hydrogels from an aqueous solution of gelatin and carboxymethyl chitosan were prepared by radiation-induced cross-linking at ambient temperature for wound healing [122]. Also, Tran et al. [123] reported an in situ-forming rutin-releasing chitosan hydrogel as an injectable dressing for wound healing.

The hydrogels derived from chitosan have been the most widely used biomaterials for tissue engineering. As tissue and organ loss or damage is a major human health problem, tissue engineering is one of the available therapies to treat such kind of damage. Hong et al. developed a novel injectable scaffold by combining collagen-coated poly-lactide microcarriers and a cross-linkable chitosan hydrogel loaded with cartilage tissue of rabbit ear for cartilage regeneration [124]. Another novel thermosensitive hydrogel composed of chitosan and pluronic was developed by Park et al. as an injectable cell delivery carrier for cartilage regeneration [125]. Tang et al. [126] prepared injectable hydrogels composed of chitosan and methyl cellulose for cartilage tissue regeneration. The obtained hydrogel resulted in good cell viability and proliferation.

Water contamination is a pervasive and extremely serious global problem owing to the rapid development of the modern industry. Among contaminants, heavy metals are the most harmful ones due to their hazardous effects on the environment. Different methods have been proposed for the treatment of water and industrial wastewater containing heavy metals. Among them adsorption is the easiest and cost-effective way. Due to the pore-forming ability, high adsorption capacity, and three-dimensional cross-linked structure of chitosan, chitosan-based hydrogels have been the most widely used adsorbents to remove heavy metals from wastewater. Some investigations have reported about using chitosan in hydrogel structure for pollutants and heavy metal removal. Wu et al. [127] reported the preparation of porous chitosan-tripolyphosphate beads by the ionotropic cross-linking and freeze-drying that were used for the removal of Cu^{2+} ion.

In another study, Li et al. [128] prepared hydrogel beads from cellulose and chitosan that show high adsorption capacities for Cu^{2+} ion. Wang and his coworkers [129] reported chitosan-poly(vinyl alcohol) hydrogel adsorbent for the removal of Hg(II) ion. Also, chitosan-graft-γ-cyclodextrin (Ch-*g*-γ-CD) was synthesized using persulfate/ascorbic acid which was used for Cd(II) removal [130].

2.1.5 Guar Gum

Guar gum is a hydrophilic and nonionic galactomannan polysaccharide derived from the seed endosperm of the plant *Cyamopsis tetragonolobus*. It is a biodegradable, nontoxic, cheap, and easily available renewable raw material that can be widely used in pharmaceutical formulations, textile, petroleum, paper, explosive, cosmetic, food, toiletry industries [131], etc. Chemically, guar gum has a linear chain of

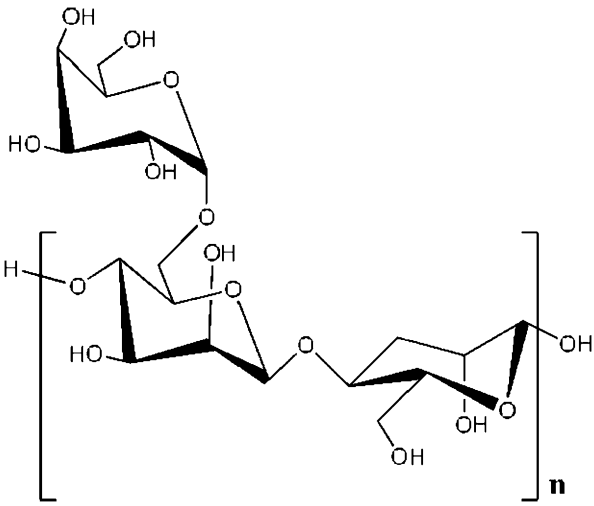

Fig. 12 Structure of guar gum [132]

(1→4)-linked β-D-mannopyranosyl units with (1→6)-linked α-D-galactopyranosyl residues as side chains with mannose: galactose ratio is approximately 2:1 (Fig. 12) [132]. The guar gum has the unique property of absorbing large quantities of water, resulting in dispersions of extremely high viscosity that makes guar gum the most applicable natural polymer nowadays. However, due to uncontrollable rate of viscosity, uncontrollable rate of hydration, instability of its solution for a long time, and susceptibility to microbial contamination restricts the use of guar gum in pharmaceutical industries. To overcome these drawbacks, a lot of research has been done to modify guar gum as hydrogel by changing their physical and chemical properties by grafting, blending, and compositing with synthetic as well as natural polymers. Some of the guar gum derivatives are carboxymethyl guar gum, hydroxymethyl guar gum, hydroxypropyl guar gum, acryloyloxy guar gum, methacryloyl guar gum, sulfated guar gum, guar gum esters [132–134], etc.

Prospects for Applications of Guar Gum-Based Hydrogels: In recent years, biopolymeric hydrogels have been receiving much more attention because of the enhanced properties over purely synthetic hydrogels [135–137]. In the pharmaceutical sector, guar gum-based hydrogel was used for the controlled release of drugs in the gastrointestinal tract, as well as carrier for colon-targeted drugs in the treatment of colorectal cancer [138, 139]. For example, Kabir and his coworkers prepared hydrogel from guar gum with glutaraldehyde and phosphate using chemical cross-linking method to be used as carrier for colon-targeted and transdermal drug delivery [140]. Moreover, M. George et al. developed pH-sensitive alginate-guar gum hydrogel cross-linked with glutaraldehyde for the controlled delivery of protein drugs.

In another study, Fujioka et al. [141] reported the synthesis of novel super-absorbent hydrogels based on the reaction of guar gum and succinic anhydride, using 4-dimethylaminopyridine as the esterification promoter demonstrating maximum absorbency in pure water.

2.1.6 Carrageenan

Carrageenan is a collective term for linear sulfonated polysaccharide that can be extracted from red seaweed (Rhodophyta), such as *Kappaphycus alvarezii*. These natural polymers comprise of repeating units of (1,3)-D-galactopyranose and (1,4)-3,6-anhydro-α-D-galactopyranose with sulfate groups in a certain amount and position [142]. Carrageenan is hydrophilic in nature due to the presence of hydroxyl groups and sulfate groups in it. Because of its gelling ability, nontoxicity, biodegradability, and biocompatibility, carrageenan is a favorable biopolymer to form hydrogel. The properties of hydrogel made from carrageenan depend on the recovery method from seaweed [142]. Alkali treatment in carrageenan recovery from seaweed improved the strength of hydrogel obtained from carrageenan [143]. Carrageenans are widely used as agent for thickening and gelling in food and nonfood industries [144].

Prospects for Applications of Carrageenan-Based Hydrogels: Hydrogels derived from carrageenan were used for various applications. Few studies reported the preparation of carrageenan-based hydrogels by cross-linking with epichlorohydrin [145] and genipin [146] that were suitable for applications in biomedical fields. As glutaraldehyde is easily available and inexpensive, Distantina et al. [147] prepared hydrogel from carrageenan by using film immersion in glutaraldehyde solution followed by thermal curing method.

At present, industry which is a huge source of water pollution produces pollutants that are extremely harmful to people and the environment. Many industries like dye, textile, paper, and plastic facilities produce considerable colored wastewater. Dyes are the type of pollutant from industry that damages the environment. So, it is necessary to remove dyes from wastewater before being discharged into the environment. Carrageenan-based hydrogels were used to remove dyes from wastewater.

Due to its high viscosity and gelling abilities, carrageenan shows interesting properties for the development of a controlled release strategy. Santo et al. [148] developed carrageenan-based hydrogel beads for the controlled delivery of platelet-derived growth factor (PDGF-BB) in bone tissue.

To improve hydrogel properties, new hydrogels based on two or more natural polymers have been developed in the last few years. For instance, Soares et al. [149] developed a new hydrogel based on two natural polysaccharides, galactomannan and kappa-carrageenan. This hydrogel was stable with possible applications in biomedical (scaffold matrices for tissue engineering) and cosmetic fields.

2.2 Protein-Based Hydrogels

Natural protein polymers, i.e., collagen, silk, gelatin, etc., can be found in plenty and offer a renewable source for production of hydrogels. These biopolymers are characterized to possess unique mechanical and architectural properties due to their homogenous secondary structure containing repetitive amino acid sequence [150]. Protein-based hydrogels offer features such as low toxicity and great biocompatibility since their chemical and mechanical structure are similar to extracellular

matrix [151]. Protein-based hydrogels show great potential in cell encapsulations [152, 153] and tissue engineering applications [154, 155]. This part will discuss about the renewable protein-based hydrogel made from biopolymers.

2.2.1 Collagen

Collagen, most common protein in mammals, has a wide application in preparing natural biomaterials. Around 25% (of dry basis) of mammalian protein matter is composed of collagen [156]. There are 28 different types of collagen [157], and among them, type I is by far the most prevalent and popular in tissue engineering owing to its facile extraction process and versatility.

Collagen is composed of a right-handed triple helical structure with amino acid triplet sequence being repeated [158]. It gives the necessary structural support and the strength to various tissues of the skin, tendons, bones, etc. by acting as the provider for adhesion molecules and growth factors [159, 160].

The most common sources are bovine or porcine origin [161]. Discarded human tissue also can be taken as a good collagen source [162]. However, collagen from mammalian tissue may carry the possibility of immunogenicity and disease transmission [163]. Recombinant collagens have low yield and high cost. Furthermore, they are often not bio-functional due to the lacking of cofactors or enzymes [163]. Hence, animal is still the principle source of collagen.

Owing to the presence in tissues, collagen hydrogels are mostly used in medical and tissue engineering, including application in the myocardium [164] and intervertebral disc [165], as a substitution of the skin [166] and regeneration of cartilage [167].

Collagen hydrogel use is limited in daily occasion since they are mechanically less stable and their degradation is rapid [168, 169]. To improve its durability and mechanical strength, collagen hydrogels are blended with natural and synthetic polymers or changing their cross-link density [170]. The hybrid hydrogels have both the trait of bioactivity of collagen and tailor-made properties of the blended polymers. Alginate, glycosaminoglycans, dextran, etc. are combined with collagen to form stable hydrogels. Collagen-alginate-dialdehyde hydrogel showed potential for cell proliferation [171]. When collagen is copolymerized with glycosaminoglycans, the hydrogel formed showed a stiffer property with a lower degradation rate [4]. Collagen gels modified with aldehyde-functionalized dextran show compressive strength around 20 times higher than pure collagen hydrogels [172]. The compressive strength can be further improved by poly(vinyl alcohol) and collagen hydrogel, cross-linking with glutaraldehyde [173]. Functionalized silver nanoparticles can also improve the tensile strength further.

For wound healing, it is necessary for hydrogels to absorb exuding wound to a significant extent. Collagen hydrogels, functionalized with 4-vinylbenzyl chloride, glycidyl methacrylate, and methacrylic anhydride individually, have shown significant high swelling with their mechanical properties being competent and cytocompatible. The swelling ratios have been found to be around 707 ± 51–1996 ± 182 wt. %. Due to the stiffness given by the vinyl group, the blended collagen hydrogels showed such characteristics [174]. Collagen-based

hydrogel nanocomposites have also been used in wastewater treatment. To absorb metal ions or dyes, hydrogels should have both ionic and nonionic functional groups. For functional group addition, natural protein polymers are grafted with vinylic moieties.

2.2.2 Silk

Silks are nonmammalian protein biopolymer with high biocompatibility and tunable biodegradability [175]. Silk proteins created from the biosynthesis of epithelial cells of insects or spiders are spun into fibers that show high thermal stability and incredible tensile strength yet being elastic [176, 177]. Hydrogels produced from silk fibers are mostly used in tissue engineering and cell encapsulation [178, 179].

Sources for silk proteins are mainly from the domesticated silkworms (*Bombyx mori*) and spiders (*Nephila clavipes* and *Araneus diadematus*) [180]. Since cultivation of a large amount of spiders are difficult and the yield is less [176], commercialization of silk proteins is mainly generated from silkworms. Generally, silkworm's silk fibers are 10–25 micrometers in diameter (Fig. 13). However, to increase the availability, the production of spider silk from bioengineered bacteria, yeast, and insects is also being explored [181].

Of the two types of components of silkworm silk proteins, fibroins are mainly used in biomaterial production. Fibroins are the structural protein, whereas the other type, sericins, which are removed during processing, glues the fibroin fibers. The presence of sericins can cause hypersensitivity in vivo [183]. Silk fibroin polymers can be transformed into hydrogel in the presence of acid, ions, or other additives [184–187]. This gelation process is due to the inter- and intramolecular hydrophobic and hydrogen bond interactions [188, 189].

Hydrogel preparation can be done in several methods (Fig. 14). They are sub-categorized mainly by physical or chemical processes. Application field of silk hydrogels is vast. Hydrogel from silk fibroin and doxorubicin, a chemotherapeutic agent, showed excellent antitumor response, better than the intravenous dosage, and that the release of doxorubicin can be controlled by modifying different properties to minimize side effects [190].

Several blended or hybrid silk hydrogels have also been successfully prepared. Silk fibroins are blended with collagens, gelatin, chitosan, etc. to form hydrogels of different characteristics. For example, gelatin and silk fibroin composite hydrogels show greater thermal withstanding at 37 °C than gelatin hydrogel alone [191]. Genipin can be used as a cross-linker to silk fibroin and gelatin blend to stabilize [192]. Changing the ratio of silk fibroin to gelatin, structural and mechanical properties of the composite hydrogel can be modulated. For the fibroin and collagen hybrid hydrogel, it has been found to have increased thermal and mechanical stability than only collagen hydrogel [193]. Hydrogels made of alginate, a natural polysaccharide, dissolve in the absence of divalent ions, thus limiting their in vivo applications. But after blending with silk fibroin, the gelation kinetics along with tailorable mechanical and structural properties of the composite could be significantly improved [194]. Composite hydrogels of silk fibroin with other synthetic

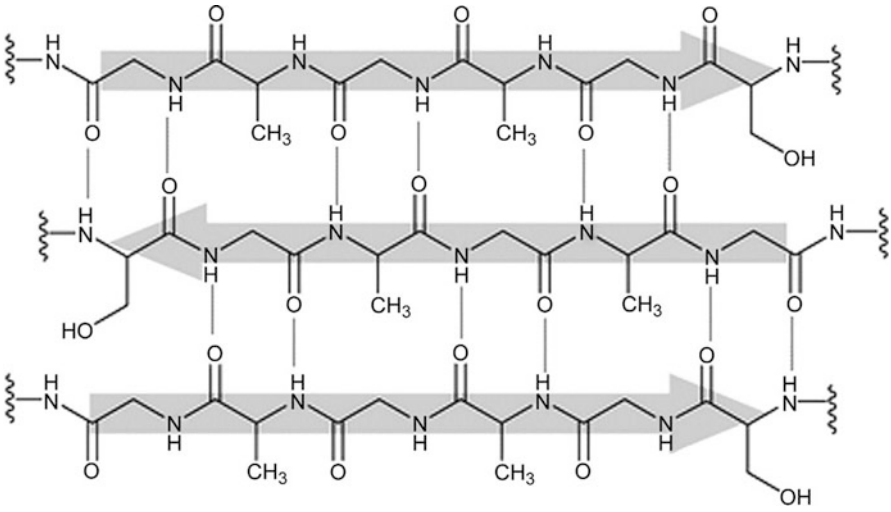

Fig. 13 Sequence of repeating amino acid units of silk. (Reprinted with permission from Ref. [182]. Copyright © 2017, Royal Society of Chemistry)

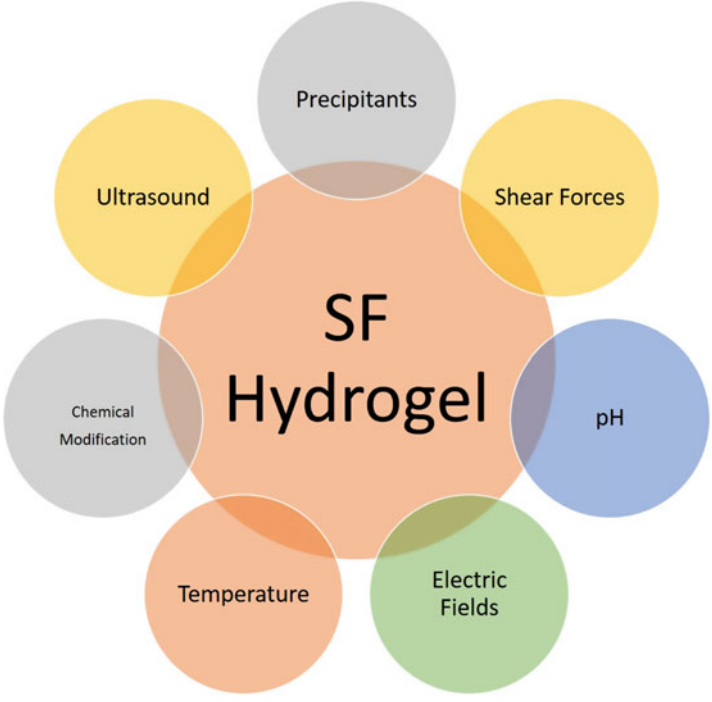

Fig. 14 Methods available for the fabrication of silk hydrogel

polymers are also being explored. Blend of silk fibroin with poly(ethylene glycol) in aqueous media and further cross-linking of the PEG macromere by means of ultraviolet rays produced a composite hydrogel that have a lower degradation temperature. In addition, due to the presence of PEG, water content of the hydrogel could also be increased. The composite hydrogel also showed increased tensile strength and elongation at break [195]. These blended hydrogels are mostly being used in biomaterials. Glycerol and silk fibroin blended hydrogels have showed a controlled release behavior of vitamin B1 derivative benfotiamine (BTMP) with the change in silk fibroin to glycerol ratio. The release of BTMP can be lowered by increasing the silk fibroin content or stiffness or glycerol content [184]. Genetically modified constructs of silk fibroin are also being studied to bring about unique characteristics. Such genetically engineered polymers have shown potential as matrices in cancer gene therapy [196].

2.2.3 Keratin

Keratin is a structural fibrous protein found in the outer layer covering of animal hairs, hooves, wool, feathers, and horns [197]. While there is an abundance of potential sources of keratin present, people often discard feathers, hairs, low-grade wools, and trimmings into waste streams.

Keratin is rich in cystine and shows good biocompatibility as well as biodegradability [199]. They have comparatively higher sulfur content. Keratin has both non-covalent and covalent interactions (disulfide bonds) (Fig. 15). These disulfide bonds help keratin to stabilize against proteolytic degradation. Furthermore, keratin compounds are not easily degradable in vivo since mammals do not produce keratinase, a keratin-degrading enzyme.

Since sources are abundant, the only cost at making keratin biomaterials comes at the processing. Extracting of keratin first starts with the breaking of disulfide cross-links between the cystines [200]. Two different methods for keratin extraction are common in which either oxidative or reductive solvents are used to create non-cross-linked keratins [201, 202]. With the oxidative solvent, cystine changes to keratose form (cysteic acid), and with reductive solvent, cystines are not affected and this form is referred to as kerateines (Fig. 16). These two forms show marked difference in degradability and mechanical structure. Although both can be used to make hydrogels, keratose can degrade relatively faster in vivo than keratin [203].

Keratin-based hydrogel scaffolds show prospect in regenerating peripheral nerves as well as promoting neuromuscular recovery [204]. Furthermore, keratin-based hydrogel was found to be neuro-inductive and promoting nerve recovery. Use of keratin hydrogel as hemostatic agent showed potential for reducing total blood loss [205]. Wool keratin hydrogels exhibited higher storage and loss modulus, i.e., faster swelling characteristics than collagen hydrogels [206]. Human hair keratin-derived hydrogel made by Ca^{2+}-induced polymerization method showed a branched and porous structure which was similar in performance to collagen hydrogels for cell viability and proliferation [207].

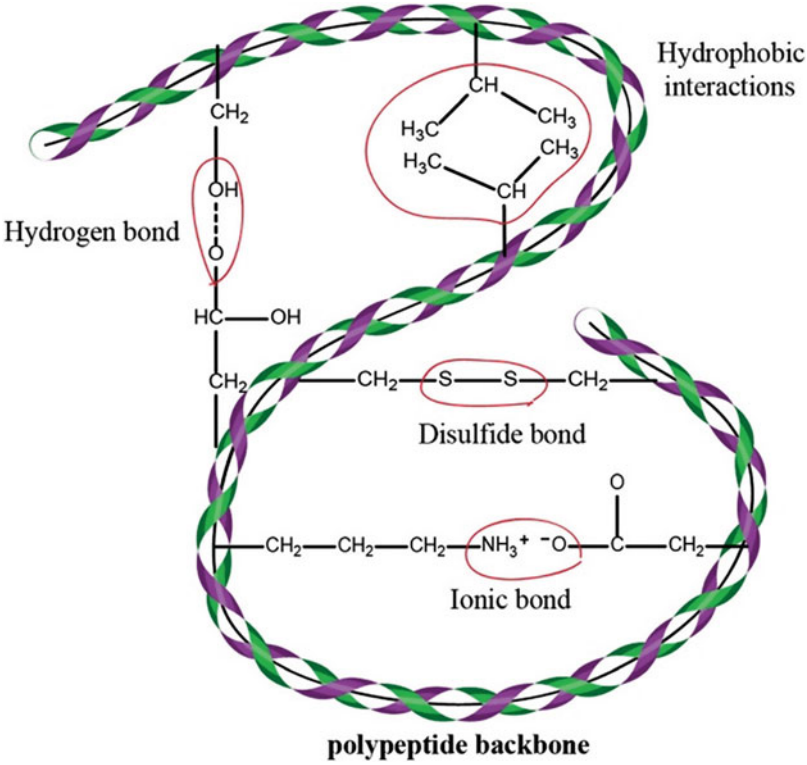

Fig. 15 Inter- and intramolecular bonding of keratin. (Reprinted with permission from Ref. [198]. Copyright © 2017, Royal Society of Chemistry)

2.2.4 Elastin

Elastin is an extracellular matrix protein often found in connective tissues of vertebrates. It is responsible for the elasticity of the skin, lungs, and blood vessels. Elastin is biosynthesized from its monomer, tropoelastin, which has both hydrophilic and hydrophobic domains [208]. The water-soluble tropoelastin monomers first aggregate at physiological state, and then cross-linking of multiple tropoelastin with lysyl oxidase forms the insoluble elastin [209]. The insolubility of elastin hinders biomaterial processing and research. To overcome this, several techniques have been adopted such as solubilization, tropoelastin utilization, and recombinant proteins.

Solubilization can be done in two forms either with oxalic acid that produces alpha-elastin or with potassium hydroxide that produces kappa-elastin. Hydrogel made of α-elastin forms through the hydrophobic interaction. Further cross-linking gives structural stability and increases mechanical properties [155, 210, 211]. α-Elastin was chemically cross-linked with glutaraldehyde at high-pressure CO_2 to form hydrogel. It has been found that with the processing pressure increased from 30 bar to 150 bar, the swelling ratio was increased 60% (Fig. 17). This cross-linked hydrogel showed sensitivity toward temperature and salt concentration change

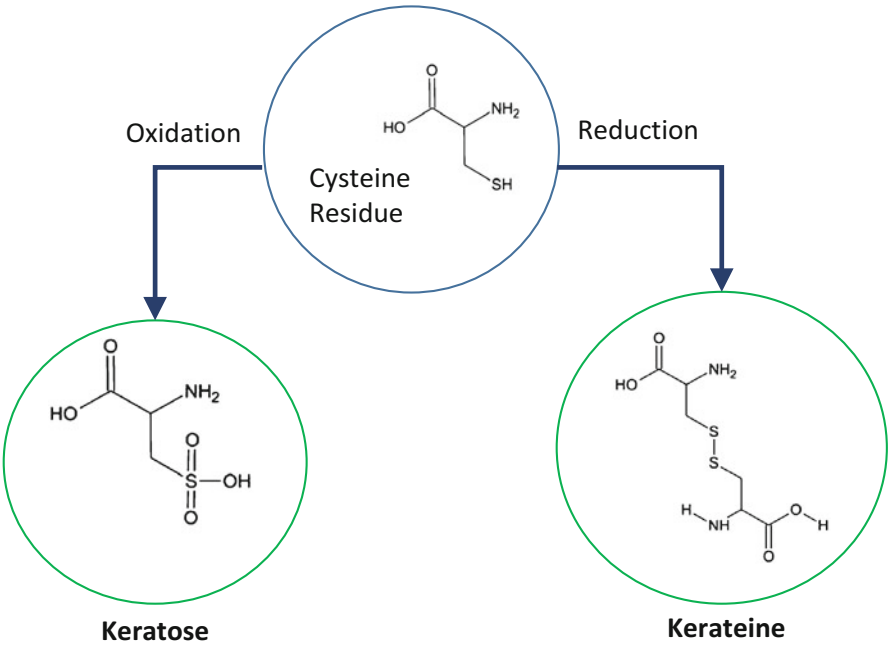

Fig. 16 Illustration depicting the process of extraction of keratose and kerateine

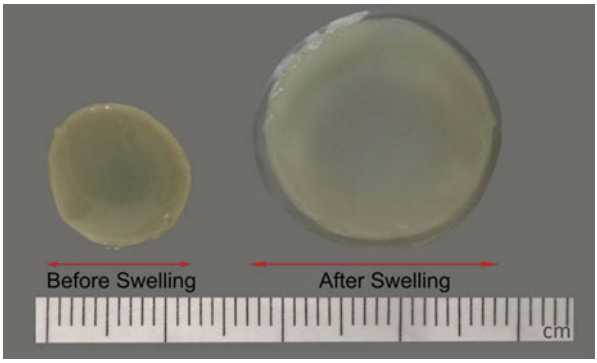

Fig. 17 Image depicting a comparison of before and after swelling of hydrogel produced at 60 bar with CO_2. (Reprinted with permission from Ref. [212]. Copyright © 2017, Elsevier)

[212]. Another hydrogel was prepared with high-pressure CO_2, cross-linking hexamethylene diisocyanate with α-elastin. The swelling ratio and porosity was also significantly improved which showed potential for tissue engineering [210]. Presently most of the elastin-based biomaterials are of elastin-like polypeptides and recombinant tropoelastin type. Mithieux et al. [213] prepared a biocompatible hydrogel by chemically cross-linking bis(sulfosuccinimidyl) suberate with recombinant human tropoelastin. The hydrogel supported in vitro epithelial and fibrosarcoma cell growth. It was also found that the hydrogel was well suited when implanted in the dorsum of guinea pigs.

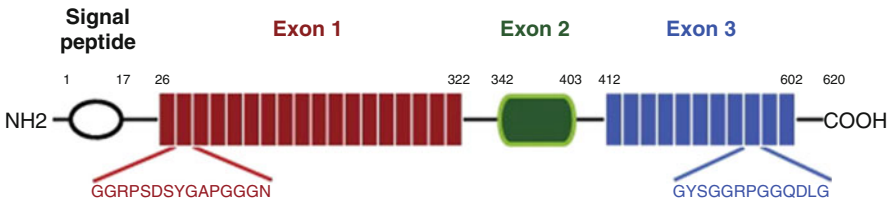

Fig. 18 Resilin gene sequence obtained from the *Drosophila melanogaster* (CG15290). (Reprinted with permission from Ref. [223]. Copyright © 2017, Elsevier)

Elastin-like polypeptides (ELP) are artificial polypeptides inspired by the disordered domains of tropoelastin [214]. Genetically modified ELPs are often used for tissue engineering. For example, ELP and poly(ethylene glycol) (PEG) were used to make a hybrid hydrogel that showed improved transparency, and when encapsulated with human fibroblasts, this hydrogel showed high viability [215]. Another study shows that ELP which was modified by the inclusion of thiols to allow disulfide bond formation formed hydrogel when exposed to UV light. This functionalized ELP showed potential as an in vivo hemostat. However, without denaturing, isolation of soluble elastin polypeptides is difficult and not suitable for mass production. To overcome this, sources like fish elastin are being explored to make elastin-based biomaterials [216].

2.2.5 Resilin

Resilin is a high resilient elastomeric protein found in insect cuticle, having high strain and low stiffness [217, 218]. Highly stretchable, resilins have elastic modulus of around 600–700 kPa. It has been shown that it can be stretched up to threefold to its original length before breaking [219]. Insect resilins are there to help insects take flight, jump, make sound, and expand exoskeleton [220, 221].

Resilin was first discovered in 1960 by Weis-Fogh [222]. Resilins are supposed to be highly disordered with presence of little to almost none secondary structures such as α helices or β sheets.

Most resilins are supposed to have three parts of exon where the first exon and third exon contain tyrosine residues which are probably responsible for cross-linking. These two exons also contain high glycine amount supposed to be involved in imparting flexibility. The second exon is known to bind chitin. This part allows the strong interaction between chitin and resilin when cuticle composite is being constructed [224, 225]. Exon I is more hydrophilic and aggregate to fibrillary structures in water, whereas exon II and exon III are relatively hydrophobic and form micelles. Dragonflies, however, do not have the chitin-binding domain in their resilin gene but just one exon [226]. Since there are not many viable ways to extract large quantities of resilin from natural sources, resilin genes have been expressed in recombinant forms. A tentative resilin gene (CG15920) was identified by Ardell and Andersen within *Drosophila melanogaster* (Fig. 18). Elvin et al. prepared a high resilient rubbery hydrogel by cross-linking a soluble protein found by cloning the first exon [227]. It has been found that resilience of around 92% was achieved in the

cross-linked resilin hydrogen with better elasticity than many other polymer hydrogels [228]. After this breakthrough, many genetically engineered resilin-like biomaterials have been studied. Charati et al. [229] removed the tyrosine with phenylalanine to enhance photochemical cross-linking. Qin et al. prepared hydrogels from exon I to exon III. The former showed a resilience of around 90%, whereas the latter showed only 63% [230]. Since resilin has great elastomeric properties, its application in cardiovascular tissue engineering is also being explored. Successful encapsulation of human aortic adventitial fibroblasts has been done in resilin-like polypeptides (RLP) and polyethylene glycol hybrid hydrogels [231]. RLP hydrogels cross-linked with tris(hydroxymethyl) phosphine showed potential for human mesenchymal stem cell encapsulation. The hydrogel could sustain its mechanical integrity and viability [232]. Hybrid hydrogel formed by ruthenium-mediated photo-cross-linking method combining regenerated silk fibroin with the recombinant resilin synthetic polymer synthesized from first exon (Rec 1) showed improved water uptake. Here the hydrogel showed improved storage modulus of around 6.56 MPa that is much higher than Rec 1 hydrogel [233].

2.2.6 Gelatin

Gelatin, a denatured protein obtained from thermal, physical, or acid and alkaline processing of collagen, has low immunogenicity, low cytotoxicity, and a great potential for biocompatibility [234–238]. Due to such properties, gelatin has been used in biomedical and pharmaceutical fields such as drug delivery, tissue engineering, biological glues [239], etc.

Source and type of collagen from which the gelatin is prepared will have influence on the properties of that gelatin. The amino acid sequence varies in sources. To elaborate, the contents of prolines and hydroxyprolines in collagens, influenced by temperature, vary from one source to another, hence the variation in gelatin properties such as denaturation temperature, thermal shrinkage, and melting temperature [240]. The sources of gelatin are mainly bovine hide and pigskin. Since mammalian sources contain transmittable diseases, other sources of gelatin are also getting popular, such as gelatin from fish sources [241]. Fish gelatins have found to have lower impact on humans than cowhide-sourced gelatins.

Gelatin hydrogel by physical cross-linking in water can be prepared above a certain concentration (around 2% w/v) and below 30–35 °C [243, 244]. That is when the gelatin-water mixture is above its gelling point temperature (around 30 °C), it exists as a sol. For the preparation of making hydrogel, the temperature is decreased below, and the gelatin monomers start to aggregate due to hydrogen bonding. The oligomers form a random conformation. At lower temperature, the hydrogen bonding shifts the random conformation to a structured one, resulting from single to triple helices which in effect make the sol-gel transformation (Fig. 19). These bonds are physical (hydrogen bonds and van der Waals), and hence the transformation is thermo-reversible [245, 246]. However, at temperature higher than 30–35 °C, these bonds are easily broken. So the resulting formation of gelatin, at higher temperature, has the possibility of change of shape as well as poor mechanical strength and low elasticity [247].

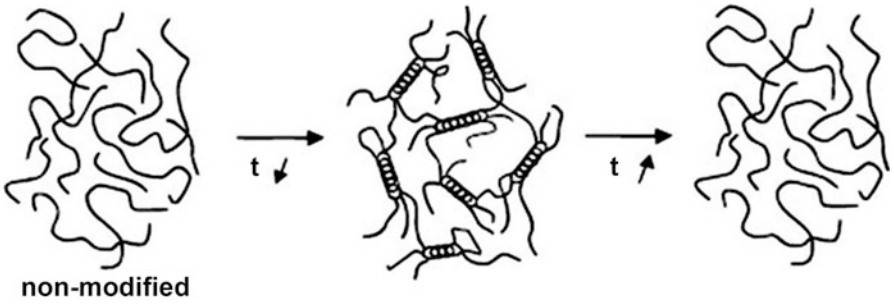

Fig. 19 Sol-gel transformation of gelatin. (Reprinted with permission from Ref. [242]. Copyright © 2017, American Chemical Society)

To use in biomedical applications with stable architectural and mechanical properties, gelatin hydrogels are covalently bonded with chemicals such as amide bond formation [248, 249]. Gelatins are often modified with methacrylate group. However, they possess short degradation time [250, 251]. To improve the degradation time and mechanical strength, photoreactive double bonds have been proposed to incorporate during hydrogel preparation [251]. Poly(lactic-co-glycolic acid) microsphere-incorporated gelatin hydrogel has shown to improve the tensile strength. To improve the elastic modulus, gelatin-poly(2-hydroxyethyl methacrylate) (PHEMA) hydrogels have been prepared. With the increase of PHEMA, the elastic modulus was found to be enhanced [252].

The potential of gelatin hydrogels for cartilage tissue engineering has been explored by modification of amino, hydroxyl, and carboxyl groups in gelatin molecules. Gelatin hydrogel has also shown potential as a drug carrier. Gelatin hydrogel incorporated with cellulose nanocrystals (CNC) has been reported to have greater sensitivity toward pH and temperature change [253]. Glutaraldehyde was used as the cross-linker to gelatin-CNC hydrogel due to its reactivity toward amine groups on gelatin.

3 Acrylate- and Acrylamide-Based Hydrogels

Acrylate and acrylamide are water-soluble synthetic monomers and are commonly used for synthesis of cross-linked polymeric hydrogel. There are several methods of preparing hydrogels from the acrylate and acrylamide monomers of which free radical cross-linking copolymerization is the most followed method where the hydrophilic monomers are reacted with cross-linkers [254].

Polyacrylamide- and polyacrylate-based synthetic hydrogels are synthesized mainly due to their responsiveness toward external stimuli such as pH, temperature, etc. pH-responsive hydrogels have either acidic or basic functional groups which accept or donate protons when there is a change in pH of the environment. Pourjavadi and Hosseinzadeh [255] synthesized a pH-sensitive hydrogel in two

stages. In the first stage, acrylamide and acrylonitrile were copolymerized using ammonium persulfate, and in the second stage, the copolymer was hydrolyzed and cross-linked. Steady swelling of the hydrogel with the increase of pH (from 1.0) occurred up to around pH 8.0 and decreased thereafter. Li et al. [256] prepared polyacrylamide-based pH-sensitive hydrogels that showed reversible swelling-deswelling behavior between pH 5.0 and 10.0. Swelling hindrance at low pH was attributed due to protonation of carboxylic groups present in the surfmar. One of the drawbacks of synthetic pH sensitive hydrogels is their non-biodegradability [257]. This could be a serious issue when the hydrogels are used inside the body for a prolonged period which can result in complications such as acute inflammation [258].

Thermosensitive synthetic acrylate- and acrylamide-based hydrogels are often in use for drug delivery; among them poly(*N*-isopropylacrylamide) (PNIPAAm) is the most common [257]. Tokuyama and Yazaki [259] prepared the PNIPAAm hydrogel using a novel circulation polymerization technique. In this process, pre-gel aqueous solution is added into moving silicon oil. Although PNIPAAm has widespread use as a temperature-sensitive hydrogel, it has certain restrictions owing to the limitation of biocompatibility of its monomers and cross-linkers used [257]. The hydrogel itself is non-biodegradable, and it activates platelets when in contact with blood [260]. Hence, use of such acrylamide-based hydrogel needs to be tested for toxicity.

Synthetic hydrogels are also applied in drug delivery. When loaded with caffeine, hydrogels synthesized from methyl methacrylate and *N*,*N*′-dimethylaminoethyl methacrylate copolymers showed release behavior at pH around 3–5 which helps the drug release in the stomach rather than on the mouth since the mouth has a neutral pH level [261]. Copolymer hydrogel of acrylamide and itaconic acid was prepared and studied for the controlled release of paracetamol [262]. Polymers such as poly(methacrylic acid-g-ethylene glycol) [P(MAA-g-EG)] have been investigated for synthesizing glucose-sensitive hydrogel that releases insulin. However, glucose-sensitive hydrogel response is quite slow and their original states are not totally acquired after response [257].

Feng et al. [263] synthesized a hybrid hydrogel made of polyacrylamide and multiwalled carbon nanotubes for increased mechanical strength. Another study showed the preparation of a hydrogel of higher strength without the use of any chemical cross-linkers. Here acrylamide monomers were copolymerized with sodium 9- or 10-acrylamidostearic acid monomers to produce the desired hydrogel [256]. Yang et al. [264] synthesized a hydrophobic hydrogel by micellar copolymerization of base monomers (acrylamide and acrylic acid) with a hydrophobic association monomer. However, a fast and responsive hydrogel is usually required to be thin and small [257]. So the synthesis of hydrogels having a fast acting quality while maintaining their mechanical strength is a challenge.

A number of synthetic monomers have been copolymerized with acrylate- or acrylamide-based monomers to produce hydrogels for different specific applications. A photochromic hydrogel (2-hydroxyl-ethyl methacrylate-N-vinylpyrrolidone-spironaphthoxazine) using HEMA (2-hydroxyethyl methacrylate) in polymeric form (PHEMA), copolymerized with *N*-vinyl-2-pyrrolidone (NVP), has found uses

as contact lenses [265]. Highly absorbent copolymer of acrylamide-crotonic acid, in the form of rod, containing ammonium nitrate and potassium nitrate fertilizer was synthesized for agricultural use [266]. Poly(acrylamide-co-acrylic acid) hydrogels have been used in gardens and fields for soil hydration. Kim et al. [267] showed that the commercially available polyacrylamide hydrogels are modified with ionic groups and that they have minimal effect on crop life and quantity. Furthermore, authors stated that such synthetic hydrogels are fragile and showed poor performance in the context of their effect on overall plant production.

4 Advantages of Renewable Hydrogels over Synthetic Hydrogels

Due to countless advantages of hydrogels prepared from renewable sources with special properties, their application fields are huge as mentioned earlier such as regenerative medicine, drug/gene delivery, stem cell and cancer research, wound healing, tissue engineering, agriculture, water treatment, hygiene products, etc. [268–270]. The benefits of renewable hydrogels produced from renewable sources over synthetic hydrogels are enormous. On the other hand, polyacrylamide hydrogels may degrade to acrylamide and become harmful for the living (Fig. 20). Although one school of thoughts believes that the polymer hydrogel is degraded to nontoxic forms other than acrylamide, there are several experimental findings to

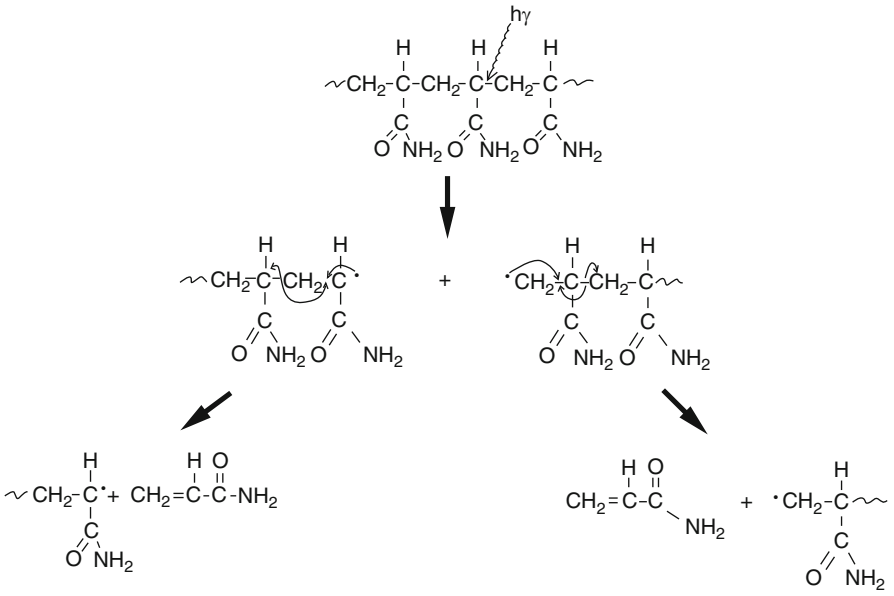

Fig. 20 Photolysis of polyacrylamide. (Reprinted with permission from Ref. [271]. Copyright © 2017, Elsevier)

prove otherwise. Smith et al. have showed that the polyacrylamide can degrade to acrylamide in the environmental condition. The researchers created an artificial environmental conditions and used ammonium concentrations and pH as parameters for the degradation of monomer/polymer. Energy from the light may break the polymers. Polyacrylamide has C-C, C-N, and C-H bonds. Crosby D.G. showed that sunrays have enough energy to break C-C bonds and thus may initiate a photolysis of polyacrylamide to form acrylamide [271]. Acrylamide is highly soluble and has the ability to translocate through various soil types. Acrylamide can cause neurotoxicity, genotoxicity, and skin irritation [272–274]. EPA has listed acrylamide as a probable carcinogen-causing compound [275]. Cationic polyacrylamides are toxic for aquatic environment and floc forming and should not be used.

Biocompatible and bioadhesive hydrogels can be prepared from renewable sources. Although most of the superabsorbent hydrogels are prepared from synthetic sources due to their lower price, the trend for replacing these synthetics with biorenewable alternatives is increasing due to the low degradability and biocompatibility of synthetic superabsorbent. One of the most important and most abundant renewable sources of hydrogel is cellulose, because it is biocompatible, biodegradable, nontoxic, and low-cost material. It has many polar hydroxyl groups, which can be applied to synthesize superabsorbent hydrogels simply with interesting valuable structures and properties. Nowadays, cellulose-based hydrogels are becoming universal and essential in many application fields [276]. By incorporating cellulose-based materials in the field of superabsorbent hydrogels, we can remove the limitations of synthetic-based superabsorbent hydrogels, and we can get products with outstanding properties [277].

But polyacrylamide hydrogels are proving to be less biocompatible than the natural renewable hydrogels. There are incidents that prove polyacrylamide hydrogel to be a less biocompatible hydrogel for human. Generally, polyacrylamide hydrogels are used as an injectable filler for soft tissue augmentation of different body areas. However, several cases of postinjection complications were recorded. Luo et al. [278] found that around 68% of 235 patients complain of pain after injecting polyacrylamide hydrogel for breast augmentation. Around 73% had multiple complications simultaneously and around 9% suffered distant gel migration. In addition, polyacrylamide deposits may worsen inflammation and infection in breast tissues by being a culture media [279]. Rong et al. [280] stated that a female patient complained of recurrent swelling and pain in temporal area after the polyacrylamide hydrogel injection. The female patient ultimately experienced leukocytopenia due to the dispersion migration of the hydrogel. Polyacrylamide may also cause complications such as acute inflammation and galactocele formation during breastfeeding [279]. Eon Rok Do showed that 10 years after injecting polyacrylamide hydrogel for breast augmentation, the patient developed lumps near the injected area [281]. Complications due to the injection of polyacrylamide hydrogels may include pain, abscess, host tissue rejection, inflammation, hematoma, etc. Delayed gel induration is also reported as a late onset of polyacrylamide [282]. Cheng et al. showed that postinjection complications may lead to breast cancer. The hydrogel may hinder the growth of fibroblasts resulting in apoptosis and hence a chance for developing cancer

[283]. Such complications show that polyacrylamide is not totally biocompatible. Furthermore, these complications may require complex surgeries and debridement procedures for cure.

5 Conclusion

This chapter presented a detail about the renewable polymer-based hydrogels, which exhibit biodegradability and biocompatibility and therefore suitable for applications in biomedical fields as well as other fields. Renewable polymers from different sources have gained a great attention of the scientists due to their intrinsic merits like low cost, eco-friendliness, biodegradability, etc. over the synthetic one during the last few decades. In this century, the demand of renewable materials is increasing in many diverse fields of basic research and different uses for the betterment of our environment. Hence, these materials are quickly developing as the sustainable replacements to non-biodegradable synthetic materials. Hydrogels from biopolymers are such kind of new materials. Throughout this chapter, it has been shown that polysaccharides have a variability and a versatility due to their special chemical structures, which is not found in other types of polymers. The uniqueness of the polysaccharides permits a very wide range of uses, and their applications can be further increased by finding new derivatives. As a result, hydrogel (from native and derived polysaccharides)-related publications and patents are increasing day by day. At the same time, renewable hydrogels from protein-based polymers are also increasing. They can form exceptional scaffolds for tissue engineering and repair due to their changeable mechanical and structural properties. Moreover, these hydrogel components are attractive for their structural tunability and precise biological functionality, and they are stimuli-responsive. Different types of synthetic hydrogels are being developed and scientists are trying to find their newer applications in biological fields. On the other hand, there are enough scientific evidences for the application of biorenewable hydrogels in the field of drug delivery and other biomedical applications. Finally, increasing the knowledge and the application of renewable hydrogels in nanoscience and nanotechnology is a potential area, which needed to be explored in the future.

6 Future Scope of Renewable Hydrogels

Among all of the renewable hydrogels, cellulose-based hydrogels are expected to be forerunners in renewable hydrogel research due to their large abundance and inherent mechanical properties. They have already showed their potentiality in waste treatment, agriculture, food packaging, and different industrial applications, where a huge amount of them are demanded. Moreover, as they are biocompatible and biodegradable materials, the importance of these hydrogels is huge in biomedical applications as well as where the environmental issues are concerned. The present trend in the development of cellulose hydrogels is to increase the safety of both the

final product and the manufacturing procedure by using nontoxic cross-linking agents or cross-linking treatments. Some hydrogels of cellulose derivatives have "smart" (sensitive to change environment like pH, ionic strength, temperature, etc.) behavior which is principally interesting for in vivo applications. Furthermore, the opportunity to functionalize cellulose-based hydrogels with bioactive and biodegradable extracellular matrix domains indicates that such hydrogels might be ideal stages for the design of scaffolding biomaterials in the arena of tissue engineering and regenerative medicine in the near future. Therefore, the advancement of the areas in chemical engineering, materials science, and biology is continuing, and it will be continuing and even larger development will occur in biomaterial research and application in the future.

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Cellulose-Based Superabsorbent Hydrogels

8

Abdulraheim M. A. Hasan and Manar El-Sayed Abdel-Raouf

Contents

Abstract

Hydrogels are polymeric three-dimensional networks able to absorb and release water solutions. Sometimes, this behavior is reversed in response to definite environmental stimuli, i.e., temperature, pH, ionic strength, etc. Such stimuli-responsive behavior makes hydrogels attractive candidates for the design of "smart" devices, applicable in a variety of technological fields. In particular, when concerning either ecological or biocompatibility issues, the biodegradability of the hydrogel network, combined with the control of the degradation rate, may add more value to the developed device. Development of new products and materials, particularly those which are based on renewable organic resources using innovative sustainable processes, represents an increasing interest in both academic and industrial research. Cellulose and its derivatives – with numerous

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hydroxyl groups – have established to be flexible materials with unique chemical structure which provides a good platform for the creation of hydrogel networks with distinctive properties with respect to swelling ability and sensibility to external stimuli. Consequently, cellulose-based hydrogels are attractive materials, biodegradable, biocompatible, and low cost, which exhibit properties that make them promising in many applications, particularly in biomedical and environmental applications. This article reviews the design and the applications of cellulose-based hydrogels, which are extensively investigated due to cellulose availability in nature, the intrinsic degradability of cellulose, and the smart behavior displayed by some cellulose derivatives.

Keywords
Cellulose · Carboxymethyl cellulose · Hydrogels · Smart polymers

1 Introduction

The modification of natural polymers is a promising method for the preparation of new materials. Graft copolymerization of vinyl monomers onto natural polymers is an efficient approach to achieve these materials. Among these materials, hydrogels have attracted great attention due to their wide applications [1–7]. Hydrogels are three-dimensional (3D) materials with the ability to absorb large amounts of water while maintaining their dimensional stability and network structure. The amount of water absorbed in hydrogels is related to the presence of specific groups such as –COOH, –OH, $–CONH_2$, –CONH–, and $–SO_3H$.

The 3D structure of hydrogels in their swollen state is maintained either by physical or chemical crosslinking [8]. These crosslinking points within the network keep the three-dimensional integrity of hydrogels in their swollen state. In chemically crosslinked hydrogels, the linear polymer chains are covalently bonded with each other via crosslinking agents; different natural polymers, either of plant or animal origin, were used in preparation of hydrogels for different applications. Some of these hydrogels are conventional hydrogels such as those used in diapers. Whereas others are "smart," i.e., they show specific response toward certain stimuli. Thus, hydrogels can be classified according to different bases. Some of these bases are given in Fig. 1.

Indeed, the invention of smart hydrogels represents a great revolution in science. Due to many environmental concerns, polymers of animal or plant sources are now incorporated in the network structure. The natural polymers derived from animal or plants are given in Table 1. The substitution of petroleum-based products with bio-based materials is not an economical solution. Some of the possible solutions are blending biopolymers with synthetic polymers and reinforcing natural fibers with synthetic polymers (termed bio-composites), which are viable alternatives to glass fiber composites.

Among natural polymers, cellulose is the most abundant organic raw material and finds numerous applications in different areas as composite materials, textiles, drug delivery systems, and personal care products. Since it was first characterized in

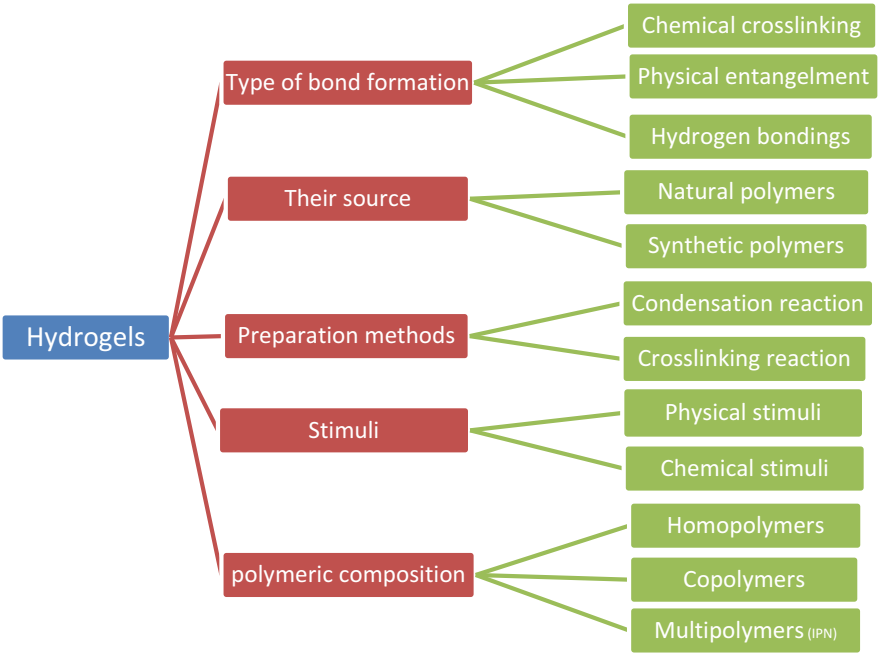


Fig. 1 Some bases of classification of hydrogels

Table 1 Natural polymers

Polysaccharides *Starch* *Cellulose* *Chitin* *Chitosan* *Guar gum*	*Proteins* *Collagen/gelatin* *Casein*, *albumin* *Fibrogen*, *silks*
Polyesters *Poly(hydroxyalkanoates)*	*Other polymers* *Lignin*, *lipids*, *shellac* *Natural rubber*

1838 [9, 10] it has received a great deal of attention for its physical properties and chemical reactivity. Moreover, cellulose is an inexpensive, biodegradable, and renewable material. Many properties of cellulose, both physical and chemical, are significantly different from those of synthetic polymers. Despite all its well-established and interesting properties, cellulose lacks some of the versatile properties of synthetic polymers.

Modification of biofibers has motivated to increase their functionality and the scope of their use. Different chemical modifications are available, but the most predominant type is modification by graft polymerization which provides a

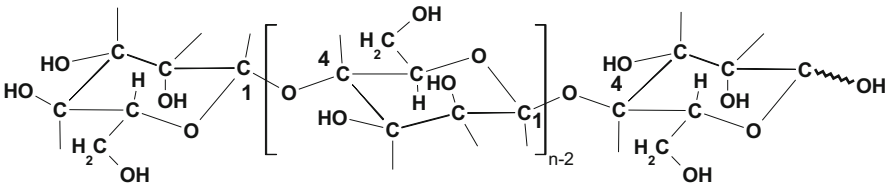


Fig. 2 Chemical structure of cellulose

means of altering the physical and chemical properties of cellulose and improving its functionality. With the recent progresses in polymer synthesis, new routes are now available for the production of functional and sustainable cellulose-based materials. In this chapter, the structure of cellulose and its reactivity, together with highlights of the recent advances in techniques for cellulose grafting, are considered.

1.1 Chemical Structure of Cellulose

The chemical and physical properties of the cellulose biopolymer are mainly dependent on its particular structure. The polymeric structure of cellulose was first verified by Staudinger in 1920. Understanding the structure of cellulose is very important in controlling its modification. Figure 2 shows the molecular structure of cellulose generated from repeating β-D-anhydroglucopyranose units that are joined together covalently through acetal functions between the equatorial group of the C4 carbon atom and the C1 carbon atom (β-1,4-glycosidic bonds).

The linearity of structure arises from the b-glucose link at C1–O–C4 to yield cellobiose units. This linear structure can contain up to 1000–1500 b-glucose units [11]. The degree of linearity enables the molecules to draw near together. Thus, cellulose has a high cohesive energy that is greatly enhanced by the fact that the hydroxyl groups are capable of forming extensive hydrogen bond networks between the chains and within the chains.

1.2 Cellulose Reactivity

The presence of three hydroxyl groups in each glucose residue gives cellulose high reactivity. In the most cases, the hydroxyl groups at the second and third positions act as secondary alcohols, while the hydroxyl group in the sixth position behaves as a primary alcohol (Fig. 3). These hydroxyl groups are principally responsible for the chemical reactions and chemical modification of cellulose.

As the DS indicates the average number of reactive groups in the molecule that have been substituted, one can say that the DS of the anhydroglucose unit

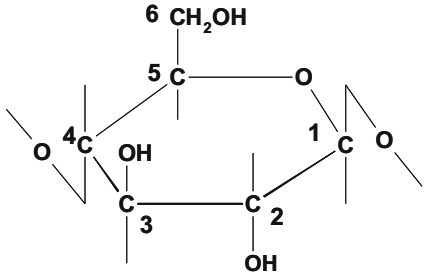


Fig. 3 The numbering system for carbon atoms in anhydroglucose unit of cellulose molecule

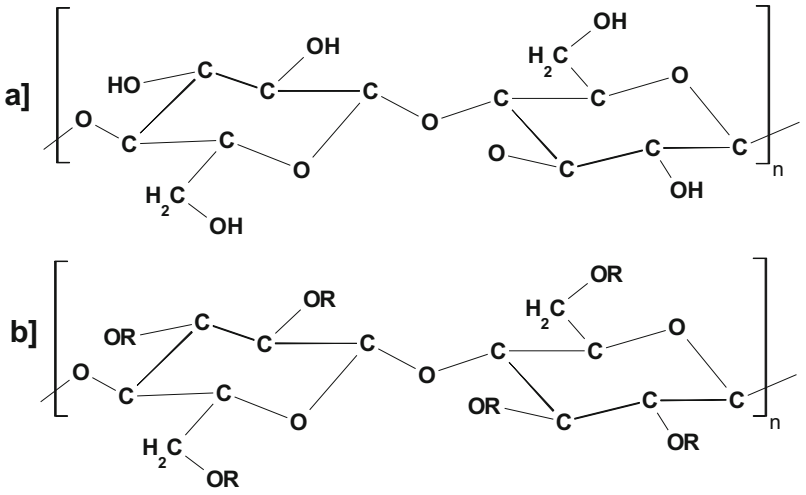
of the cellulose molecule is three [12]. However, the reaction of cellulose should not simply be considered as being that of a trihydric alcohol that is similar in its chemistry to trihydric sugar. This is due to that cellulose is a fiber-forming and a high molar mass substance. The reactivity of these three hydroxyl groups under is mainly affected by their intrinsic chemical reactivity, by steric effects that are produced by the reacting agent, and by steric effects that are derived from the supramolecular structure of cellulose. Generally, the relative reactivity of the hydroxyl groups can be expressed as OH–C6 $\gg$ OH–C2 $>$ OH–C3 [13, 14].

2 Chemical Modification of Cellulose

Cellulose is a distinctive natural polymer that possesses several attributes such as a fine cross section, the ability to absorb moisture, high strength and durability, high thermal stability, good biocompatibility, relatively low cost, low density, and good mechanical properties [14]. Yet, there are some drawbacks for cellulose. These include poor solubility in common solvents, poor dimensional stability, lack of thermoplasticity, and lack of antimicrobial properties. Thus controlled physical and/or chemical modification of the cellulose structure is necessary to prevail over such drawbacks [15].

Introducing functional groups into cellulose molecules through chemical modification is one of the key ways of adding new properties to the cellulose without destroying its many attractive intrinsic properties. For instance, the formation of cellulose nitrate involves the esterification of cellulose with nitric acid in the presence of sulfuric acid, phosphoric acid, or acetic acid. Currently, other commercially important cellulose derivatives include hydroxyl ethyl cellulose, carboxymethyl cellulose, etc. Some cellulose derivatives are given in Fig. 4.

The modification of cellulose with bi- or polyfunctional compounds to form crosslinked or network structure provides another possible attempt of modifying the structure of cellulose [16]. These methods can bring stability to the structure of cellulose and can induce crease-resistance (or “durable press” properties) to cellulose [17]. Among the methods of modification of polymers, graft copolymerization offers a smart and adaptable means of imparting a range of functional groups to



MC	R= H, CH_3
HPMC	R= H, CH_3, $CH_2CH_2CH(OH)\ CH_3$
EC	R= H, CH_2CH_3
HEC	R= H, CH_2CH_2OH
NaCMC	R= H, CH_2COONa

Fig. 4 (**a**) Repeating unit of cellulose "cellobiose." (**b**) Repeating unit of cellulose derivatives. The substituent group "R" is indicated for (MC), (HPMC), (EC), (HEC), and (NaCMC)

a polymer molecule. A graft copolymer generally consists of a long chain of one monomer, referred to as the backbone polymer (main chain) with one or more branches (grafts) of long sequences of a different monomer [18].

This chemical modification can provide polymeric materials with valuable properties and different chemical structures. It can also permits one to combine the best properties of two or more polymers in one physical unit This can be achieved by controlling some parameters such as the polymer types, the degree of polymerization and the polydispersities of the main chain and the side chains, the graft density (average spacing in between the side chains), and the distribution of the grafts (graft uniformity) [19].

The creation of cellulose graft copolymers is one of the key ways of modifying the physical properties and chemical properties of cellulose [19]. This involves modification of the cellulose molecules through the formation of branches (grafts) of synthetic polymers that impart specific properties onto the cellulose substrate, without destroying its intrinsic properties (Fig. 5). These grafts can be linked together via their functional groups to form a three-dimensional network structure known as "gel." Cellulose hydrogels will be discussed in more details in the next sections.

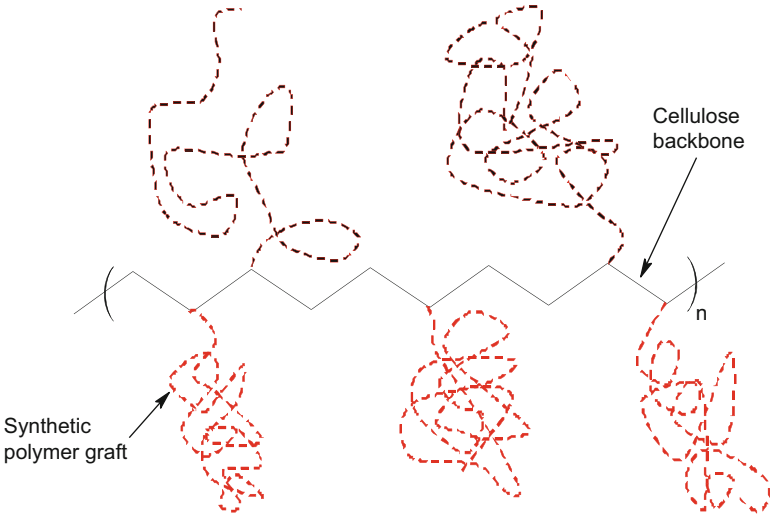


Fig. 5 An illustration of cellulose graft copolymer

Table 2 The most common cellulose derivatives

Cellulose derivatives	Applications	Ref.
Carboxy methyl cellulose	Biomedical and agriculture	[22, 23]
Methyl cellulose	Releasing fertilizers	[24, 25]
Hydroxy ethyl cellulose	Smart materials	[26, 27]
Hydroxypropyl methyl cellulose	Controlled release	[28, 29]
Cellulose acetate	Drug carrier system	[30, 31]

3 Cellulose-Based Smart Hydrogels

Because cellulose has many hydroxyl groups which can form hydrogen bonding linked network easily, various designations of cellulose-based hydrogels can be tailored. Water-soluble cellulose derivatives are mostly biocompatible which can be used as thickener, binding agents, emulsifiers, film formers, suspension aids, surfactants, lubricants, and stabilizers, especially as additives in food, pharmaceutical, and cosmetic industries.

Cellulose-based hydrogels can be obtained via either physical or chemical stabilization of aqueous solutions of cellulosics. Additional natural and/or synthetic polymers might be combined with cellulose to obtain composite hydrogels with specific properties [20, 21]. Some cellulose derivatives and their most common applications are given in Table 2.

Stimuli-responsive or smart hydrogels are those hydrogels that undergo reasonably large and abrupt changes in their network structure, swelling behavior,

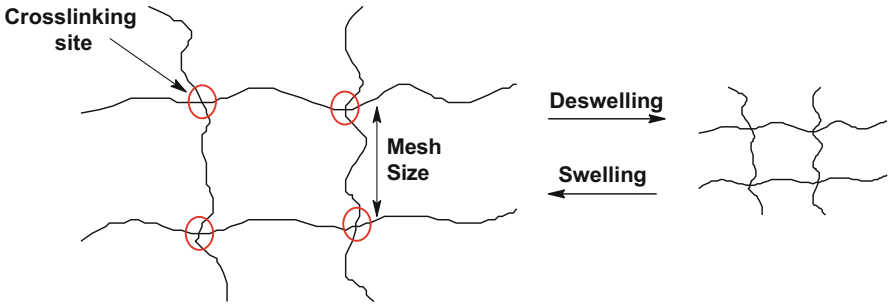


Fig. 6 Stimuli-responsive hydrogel

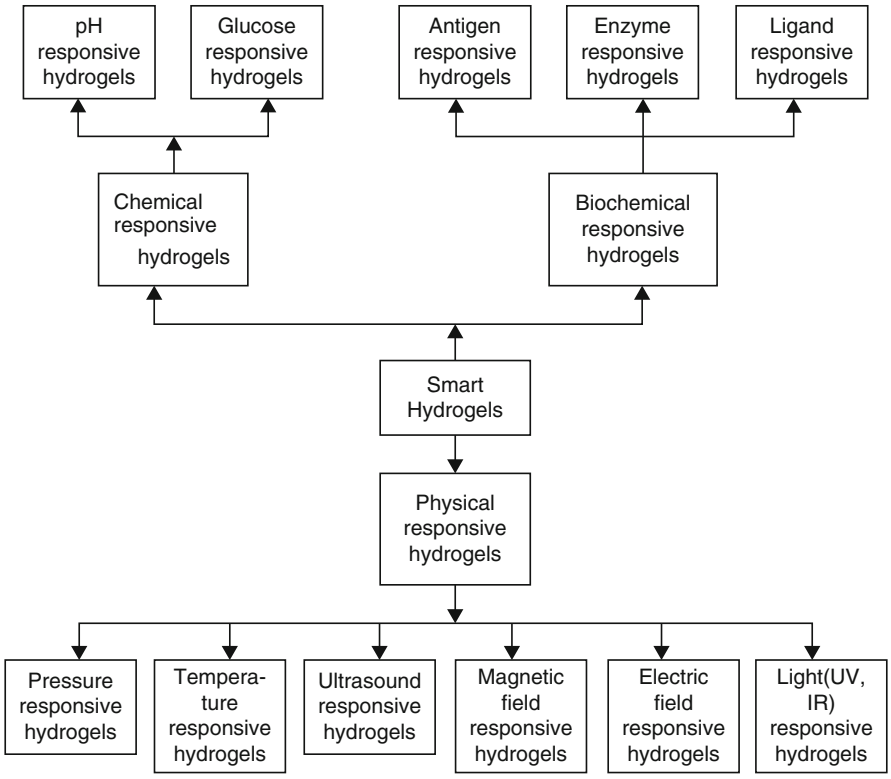


Fig. 7 Classification of smart hydrogels. (Modified from [34])

permeability, and/or mechanical strength in response to small environmental changes (Fig. 6). Stimuli-responsive hydrogels are also known as environmentally sensitive hydrogels [32, 33]. Stimuli-responsive hydrogels could be further classified as either physical or chemical stimuli-responsive hydrogels as shown in Fig. 7 [34]. Chemical

stimuli, such as pH, ionic factors, and chemical agents, change the interactions between polymer chains or between polymer chains and solvent at the molecular level, whereas physical stimuli, such as temperature and electric or magnetic fields, and mechanical stress will influence the molecular interactions at critical onset points.

3.1 Thermo-Responsive Cellulose-Based Hydrogels

Temperature-responsive hydrogels have gained considerable attention in the endless applications. Some molecular interactions, such as hydrophobic associations and hydrogen bonds, play a vital role in the immediate volume change of these hydrogels at the critical solution temperature (CST). In the swollen state, water molecules form hydrogen bonds with polar groups of polymer backbone within the hydrogels and arrange themselves around hydrophobic groups.

Physically crosslinked, thermo-reversible gels were prepared from water solutions of methylcellulose and/or hydroxypropyl methylcellulose (in a concentration of 1–10% by weight) [21]. The gelation mechanism involved hydrophobic associations among the macromolecules possessing the methoxy group. At low temperatures, polymer chains in solution are hydrated and simply entwined with one another. By increasing temperature, water of hydration is lost gradually, until polymer-polymer hydrophobic associations take place, thus forming the hydrogel network.

The glass transition temperature (Tg) was dependent on the degree of substitution of the cellulose ethers as well as on the addition of salts. A higher degree of substitution of the cellulose derivatives provided them a more hydrophobic character, thus reducing the glass transition temperature at which hydrophobic associations take place. A similar effect was noticed when adding salts to the polymer solution. This may be due to that salts reduce the hydration level of macromolecules by recalling the presence of water molecules around themselves. Both the degree of substitution and the salt concentration could be properly adjusted to obtain specific formulations gelling at 37 °C and thus potentially useful for biomedical applications [35–37].

Selective cellulose derivatives, including methyl cellulose (MC), hydroxypropyl cellulose (HPC), hydroxypropylmethyl cellulose (HPMC), and carboxymethyl cellulose (CMC), have been used to construct cellulose-based hydrogels through physical crosslinking and chemical crosslinking. The mostly studied temperature-responsive hydrogels among cellulose derivatives were methylcellulose [38] and hydroxypropyl methylcellulose [39].

In the case of physical crosslinked gels, there is no covalent bonding formation or breakage, and the crosslinked network is formed through ionic bonding, hydrogen bonding, or an associative polymer-polymer interaction [40]. In general, chemical crosslinked hydrogels are prepared through crosslinking two or more kinds of polymer chains with a functionalized crosslinker [41] or under UV light [42]. However, physically crosslinked hydrogels are reversible [39] thus might flow under given conditions (e.g., mechanical loading) and might degrade in an uncontrollable manner. Due to such drawbacks, physical hydrogels based on MC and

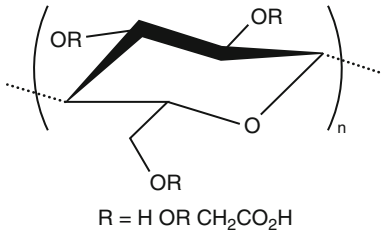


Fig. 8 Chemical structure of CMC

HPMC are not recommended for use in vivo. In vitro, MC hydrogels have been recently proposed as novel cell sheet harvest systems [43].

In agriculture, there is an increasing interest in using superabsorbent hydrogels. This is mainly due to the call for a reduction of water consumption and to optimize water resources in agriculture and horticulture and has a role in the endorsement of a novel advance of human habit and culture toward water, to be treated as a benefit to save and not as an excess to waste. During the swelling process of a superabsorbent hydrogel, the material changes from a glassy to a rubber-like state, which is able to pile up large amount of water and release the stored water under significant conditions. The controlled release system is formed from carboxymethyl cellulose (Fig. 8), a low-cost and completely biocompatible polymer that can be produced in a sustainable way from natural sources.

In this respect, Bao et al. [44] investigated the reaction process of cellulose-based inorganic/organic nanocomposite superabsorbent hydrogels by solution polymerization. First, potassium persulfate was used as an initiator to produce free radicals under heating, and then these radicals abstracted hydrogen from the hydroxyl groups on the cellulose substrate to create the alkoxy radicals. The alkoxy radicals attacked the acrylic monomers leading to chain initiation. Consequently, these small molecule radicals acted as free-radical donors to the neighboring molecules. Furthermore, in the presence of the crosslinker, *N*,*N*- methylenebisacrylamide (MBA), and a filler, inorganic sodium montmorillonite (Na-MMT), the chain propagation developed promptly. Finally, the reaction ceases by the coupling of macromolecules. The formation mechanisms of cellulose-g-poly(AA-co-AM-co-AMPS)/MMT superabsorbent hydrogel are shown in Fig. 9.

During or after preparation, the xerogel might also be loaded with nutrients and/or plant pharmaceuticals. When irrigating plants, the water is absorbed by the hydrogel, which then affected externally to release water and nutrients to the soil as needed, thus keeping the soil moist over long periods of time. This process is a highly water-saving process that the water is not lost soon after the watering due to evaporation and drainage and a redistribution of the water resources available for cultivation in other applications [45–47]. An extra advantage in using hydrogels in this application is related to the effect of the swelling itself on the soil. Indeed the hydrogel granules, which in the dry form have almost the same dimensions of the substrate granules, increase their dimension after swelling, thus increasing soil porosity and providing a better oxygenation to the plant roots (Fig. 10) [45].

This also suggests that large-granule hydrogels are likely to yield better results than fine-granule ones, if suitably mixed with the soil (indeed different spatial

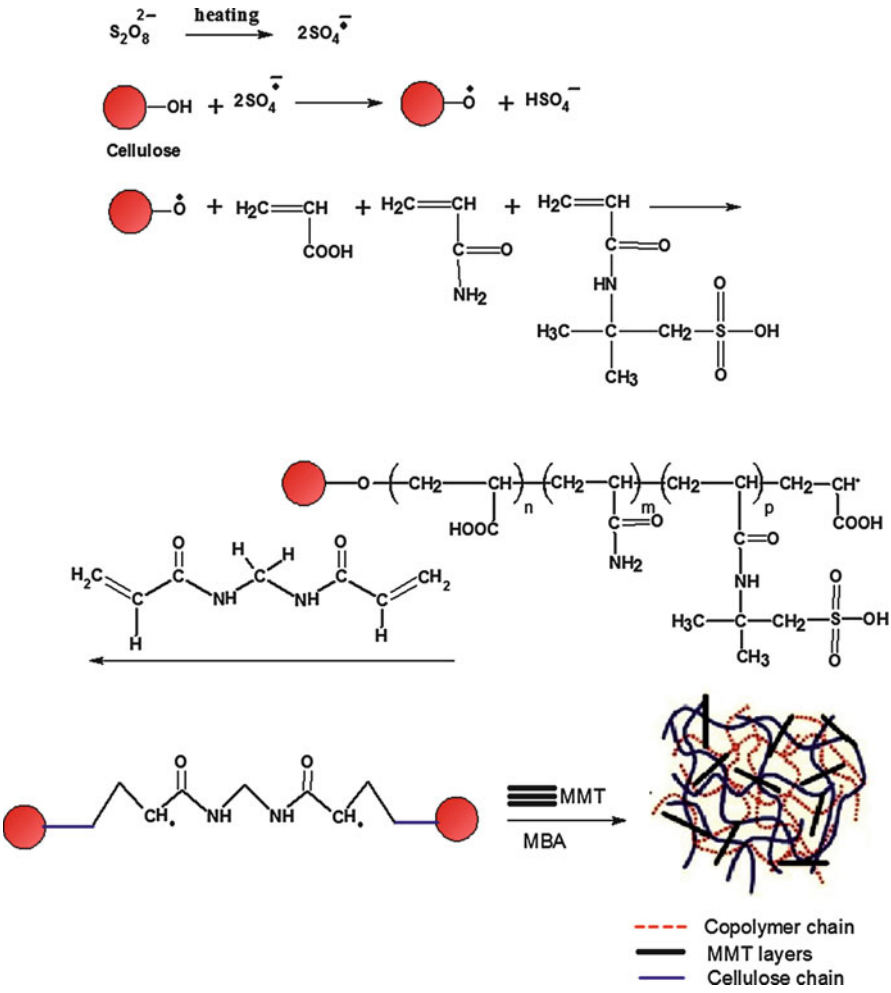


Fig. 9 Mechanism of formation of CMC-based superabsorbent hydrogels

configurations for the soil and hydrogel particles are possible, depending on their densities and the soil-hydrogel and hydrogel-hydrogel interactions).

Cellulose-based hydrogels fit perfectly in the current trend to develop environmentally friendly alternatives to acrylate-based superabsorbent hydrogels [48–50]. Sannino and coworkers recently developed a novel class of totally biodegradable and biocompatible microporous cellulose-based superabsorbent hydrogels [47]. In biomedical applications, cellulose derivatives are used in preparation of thermoresponsive hydrogels used in drug delivery systems, as found in dressing and in bioengineering.

In this respect, Trong et al. [51] prepared hydrogel membranes mainly composed of three kinds of latex particles within carboxymethyl cellulose (CMC) matrix for

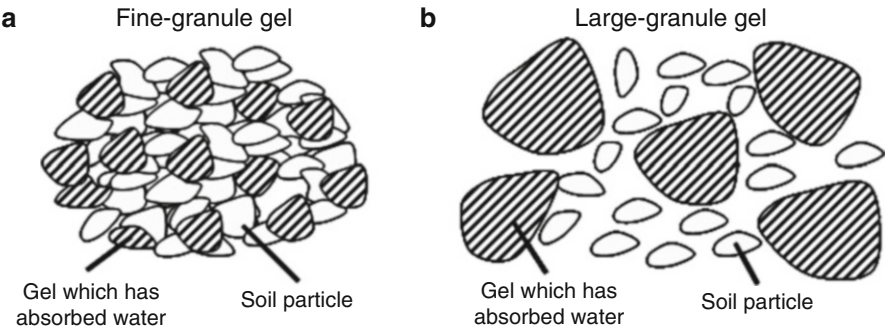


Fig. 10 Compactness of soil particles due to addition of hydrogels [45]

the purpose of transdermal drug release. To give a thermo-responsive behavior in swelling, poly(*N*-isopropyl acrylamide) latex and its copolymers were synthesized by polymerization of *N*-isopropyl acrylamide with different amounts of acrylic acid, in which lower critical solution temperature (LCST) could be modulated. Morphology, structures, and swelling capability of prepared hydrogel membranes were then examined. Caffeine, used as the model drug, was incorporated into membranes, and the drug release behavior at different temperatures was evaluated. These prepared hydrogel membranes have potential in the application of transdermal drug delivery system.

Recently, semi-interpenetrating polymer network (SIPN) strategy was employed to fabricate a kind of novel hydrogels composed of cellulose and poly(*N*-isopropylacrylamide) (PNIPAAm) in the presence of *N*,*N*-methylenebisacrylamide (MBAAm) as the crosslinker and benzoyl peroxide (BPO) as the initiator. The results from FTIR and TGA indicated that the network indeed existed in the SIPN hydrogels. The data from experiments, those associated to the swelling behavior of the hydrogels at different temperatures in particular, proved the thermal sensitivity of these hydrogels. The impact of crosslinker concentration on the hydrogel properties was discussed as well. The swelling ratio of hydrogels decreased with increasing the content of MBAAm. Besides, the loading and releasing behavior of the hydrogels was examined using dimethyl methylene blue as a model drug. These novel hydrogels combining the advantages of natural polymer with thermal-responsive behavior are of great potential to be applied to drug delivery and control release systems [52].

Mohammed and Kourosh [53] suggested the following mechanism for preparation of carbohydrate-based superabsorbent hydrogel (Fig. 11):

(a) Graft copolymerization of suitable vinyl monomer(s) on polysaccharide in the presence of a crosslinker
(b) Direct crosslinking of polysaccharide

In graft copolymerization, generally a polysaccharide enters reaction with initiator by either of two separate ways. First, the neighboring OHs on the saccharide units

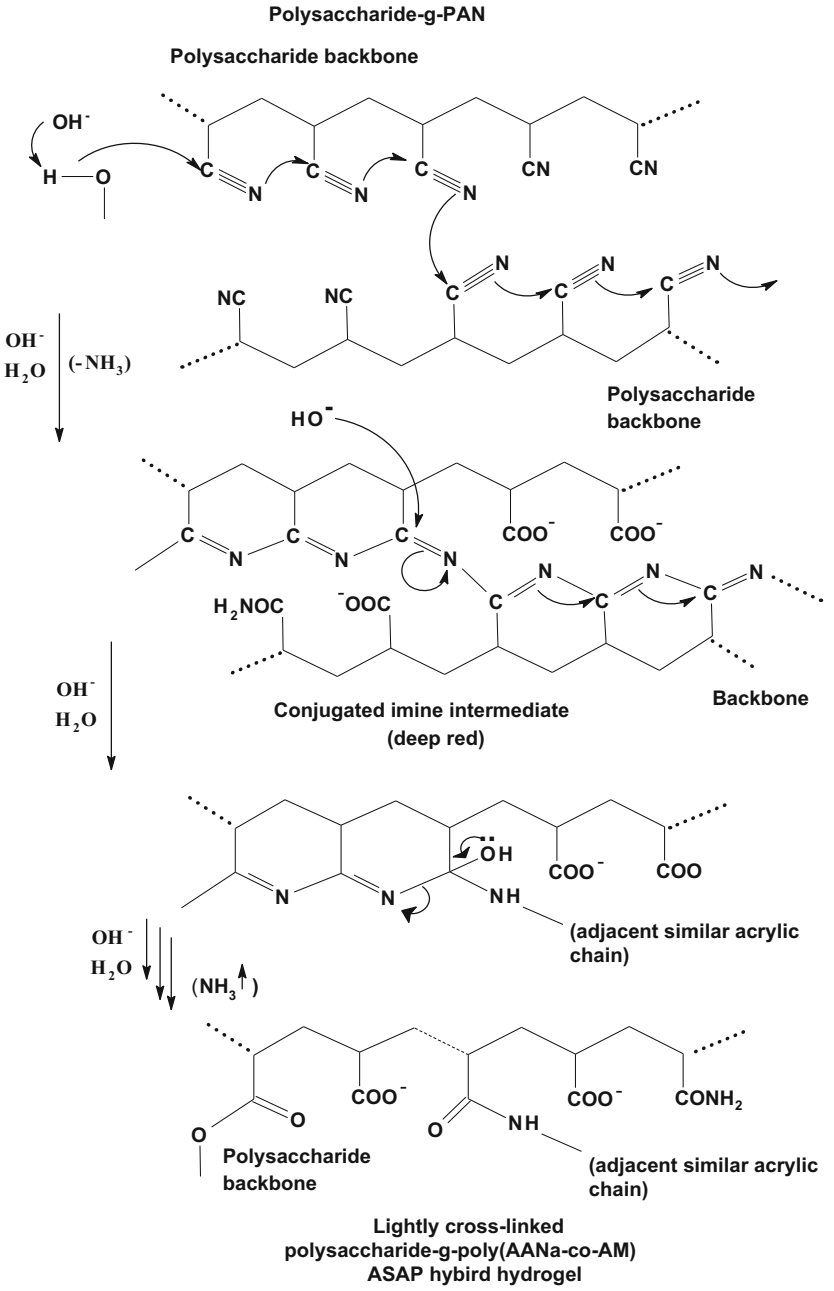


Fig. 11 The mechanism of preparation of polysaccharide-g-PAN copolymer superabsorbent

and the initiator (commonly Ce^{4+}) interact to form redox pair-based complexes. These complexes are subsequently dissociated to produce carbon radicals on the polysaccharide substrate via homogeneous cleavage of the saccharide C–C bonds. These free radicals initiate the graft polymerization of the vinyl monomers and crosslinker on the substrate. In the second way of initiation, an initiator such as persulfate may abstract hydrogen radicals from the OHs of the polysaccharide to produce the initiating radicals on the polysaccharide backbone.

Due to employing a thermal initiator, this reaction is more affected by temperature compared to previous method. In agriculture, polymer complexes of crosslinked carboxymethyl cellulose (CMC) and starch were synthesized to form superabsorbent polymers (SAP) and their performances as a water retaining aid for irrigation were assessed [54]. Starch from vegetables and chemically modified cellulose fibers were used as the basis for the polymer structure because of their biodegradability and the sustainability of their sources. These polymers were found to release the absorbed water at 34 °C, i.e., the LCST of *N*-isopropylacrylamide.

3.2 pH-Responsive Cellulose-Based Hydrogels

Variations in pH are known to occur at several body sites, such as the gastrointestinal tract [55], vagina [56], and blood vessels, and these can provide a suitable base for pH-responsive drug release. pH- sensitive polymers are polyelectrolytes that bear in their structure weak acidic or basic groups that either accept or release protons in response to changes in environmental pH. The pendant acidic or basic groups on polyelectrolytes undergo ionization just like acidic or basic groups of monoacids or monobases. However, complete ionization on polyelectrolytes is more difficult due to electrostatic effects exerted by other adjacent ionized groups. Most commonly studied ionic polymers for pH-responsive behavior include poly (acrylamide) (PAAm), poly(acrylic acid) (PAA), poly(methacrylic acid) (PMAA), poly (diethylaminoethyl methacrylate) (PDEAEMA), and poly(dimethylaminoethyl methacrylate) (PDMAEMA).

In this respect, a new set of pH-, temperature-, and redox-responsive hydrogels were prepared from carboxymethylcellulose (CMC) and poly(*N*-isopropylacrylamide). Copolymeric (CP) hydrogels were synthesized by copolymerizing *N*-isopropylacrylamide (NIPA) and methacrylated carboxymethylcellulose; semi-interpenetrating network (SIPN) hydrogels were prepared by polymerizing NIPA in the presence of CMC. Two types of crosslinkers were used, viz., *N*, *N*′-Methylenebisacrylamide (MBA) and *N*,*N*′-Bis(acryloyl)cystamine (BAC), a redox sensitive crosslinker. The structures of the hydrogels were characterized by FTIR and SEM studies. The CP hydrogels were proved to be more porous than analogous SIPNs which resulted in higher swelling for the CP hydrogels. Swelling for both the hydrogels was established to increase with CMC content. While the swelling of SIPN hydrogels showed discontinuous temperature dependency,

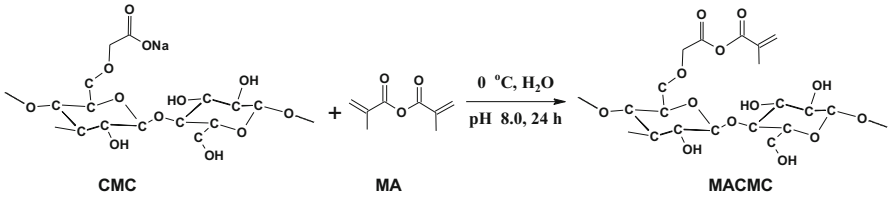


Fig. 12 Synthesis of methacrylated carboxymethyl cellulose sodium salt (MACMC)

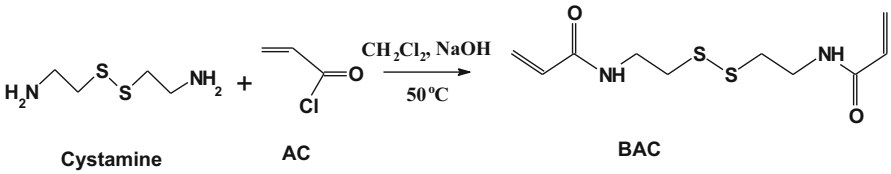


Fig. 13 Synthesis of *N*,*N*′-Bis(acryloyl)cystamine (BAC)

CP hydrogels showed gradual decrease in water retention values with increase in temperature. CBA crosslinked hydrogels showed higher swelling in comparison to BIS crosslinked hydrogels. Additionally, lysozyme was loaded in the hydrogels, and its in vitro release was studied in various pH, temperature, and in the presence of a reducing agent, glutathione (GSH). The release rate was found to be maximum at lower temperature, lower pH, and in the presence of GSH [57] (Figs. 12 and 13).

Furthermore, Lim et al. [58] prepared a novel pH-sensitive hydrogel with superior thermal stability, composed of poly(acrylic acid) (PAA) and cellulose nanocrystal (CNC). CNC was extracted from kenaf fiber through a series of alkali and bleaching treatments followed by acid hydrolysis. PAA was then subjected to chemical crosslinking using the crosslinking agent (*N*,*N*-methylenebisacrylamide) in CNC suspension. A disk shape hydrogel was obtained by casting the mixture onto a petri dish. PAA/cellulose hydrogel with the same composition ratio was also prepared as control. The effect of reaction conditions such as the ratio of PAA and CNC on the swelling behavior of the hydrogel obtained toward pH was studied. The obtained hydrogel was further subjected to different tests such as thermogravimetric analysis (TGA) to investigate the thermal behavior, Fourier transform infrared for functional group detection, and swelling test for swelling behavior at different pH. The crosslinking of PAA was established with FTIR with the the absence of C=C double bond. In TGA test, PAA/CNC hydrogel showed significantly higher thermal stability compared with pure PAA hydrogel. The hydrogel obtained showed excellent pH sensitivity and experienced maximum swelling at pH 7. The PAA/CNC hydrogel can be developed further as drug carrier.

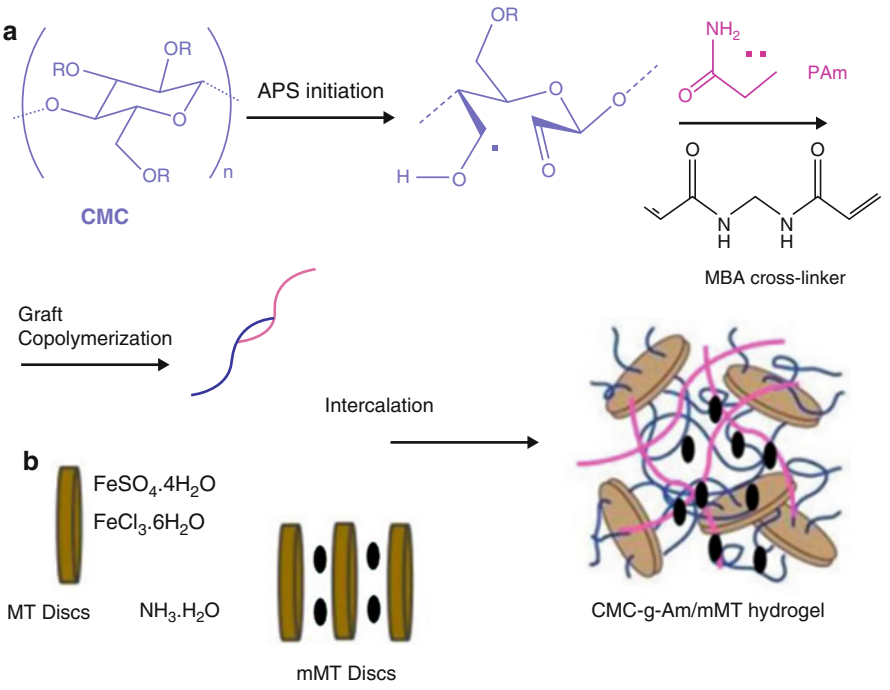


Fig. 14 Schematic representation for the synthesis of CMC-g-Am/mMT hydrogel [59]

Recently, Gholamreza et al. [59] developed magnetic/pH-sensitive nanocomposite hydrogel-based carboxymethyl cellulose-g-polyacrylamide/montmorillonite for colon-targeted drug delivery (Fig. 14).

3.3 Biodegradable Cellulose-Based Hydrogels

An important focus of the research in this field is the material's biodegradability. Modern superabsorbents are non-biodegradable acrylamide-based products. The renewed attention of institutions and public opinion toward environmental protection issues has awoken some producers to the development of biodegradable superabsorbents. Potential biodegradable cellulose-based superabsorbent, with sorption properties similar to those displayed for acrylate-based products, can be prepared by crosslinking reaction of cellulose polyelectrolyte derivatives, carboxymethyl cellulose (CMC), hydroxyethyl cellulose, etc.

Biodegradable superabsorbent hydrogels involve crosslinked poly (amino acid)s such as poly(γ-glutamic acid) and poly(aspartic acid) [60, 61] and crosslinked sodium salt of carboxymethyl cellulose (CMC). The crosslinking of CMC has been investigated with various methods, such as crosslinking agents [62] and ionizing irradiation [63, 64]. As concerns about environmental problems are rising today, various

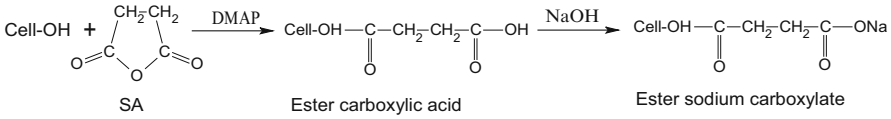


Fig. 15 Synthetic route of sodium carboxylate from cotton cellulose and SA [68]

naturally occurring polymers should be used instead of synthetic ones. Among them, cellulose exists most abundantly on the earth and is used for various applications. Cotton is one of the most accessible types of cellulose in our daily life and is produced in large amounts every year [65] One of the typical features of cotton cellulose is its extremely high molecular weight in the cellulosic family, over 1,000,000 [66]. Thus, cotton cellulose is a suitable starting material for superabsorbent hydrogels because the extremely high molecular weight of the polymer is one of the indispensable factors for attaining high water absorbency. The most representative cellulosic derivative containing sodium carboxylate is CMC, which contains it via an ether linkage [67].

The introduction of sodium carboxylate groups into cotton cellulose was investigated by esterification because esterification proceeds under milder conditions than etherification and ester linkages are more susceptible to hydrolysis and biodegradation than ether linkages [68] (Fig. 15). These features are suitable for the design of biodegradable superabsorbent hydrogels. Thus, the synthesis of superabsorbent hydrogels by the esterification of cotton cellulose with succinic anhydride (SA) was studied. It was found that a hydrogel could be obtained without any crosslinker when 4-dimethylaminopyridine (DMAP) was used as an esterification catalyst (Fig. 16).

Furthermore, Francesco et al. [69] evaluated a novel class of cellulose-based superabsorbent hydrogels, totally biodegradable and biocompatible, for agricultural use. Briefly, two cellulose derivatives, sodium carboxymethyl cellulose (CMCNa) and hydroxyethyl cellulose (HEC), were used for superabsorbent hydrogel preparation; citric acid (CA), a crosslinking agent able to overcome toxicity and costs associated with other crosslinking reagents, was selected in a heat-activated reaction. The objectives of their study were (1) to validate the ability of the hydrogel to modify the water retention properties of the growing media (soils and soilless substrates), (2) to investigate the effects on the growth of plants grown on media amended with the hydrogel, and (3) to find out the biodegradability of the prepared hydrogels. The applied tests revealed the absence of phytotoxicity of the hydrogel, and cultivation trials on cucumber (on soil) and sweet basil (in soilless conditions) showed a general overall enhancement of plant growth and quality when hydrogel was added to growing media. The tested hydrogel showed a high suitability for potential use in agriculture. The scheme for crosslinking reaction is illustrated in Fig. 17 [70].

Chunyu et al. demonstrated [71] two novel methods to prepare cellulose/PVA hydrogels with different functional properties via a green process. They introduced a series of hydrogels that were prepared from cellulose and PVA in NaOH/urea aqueous solution using both physical and chemical crosslinking methods. The

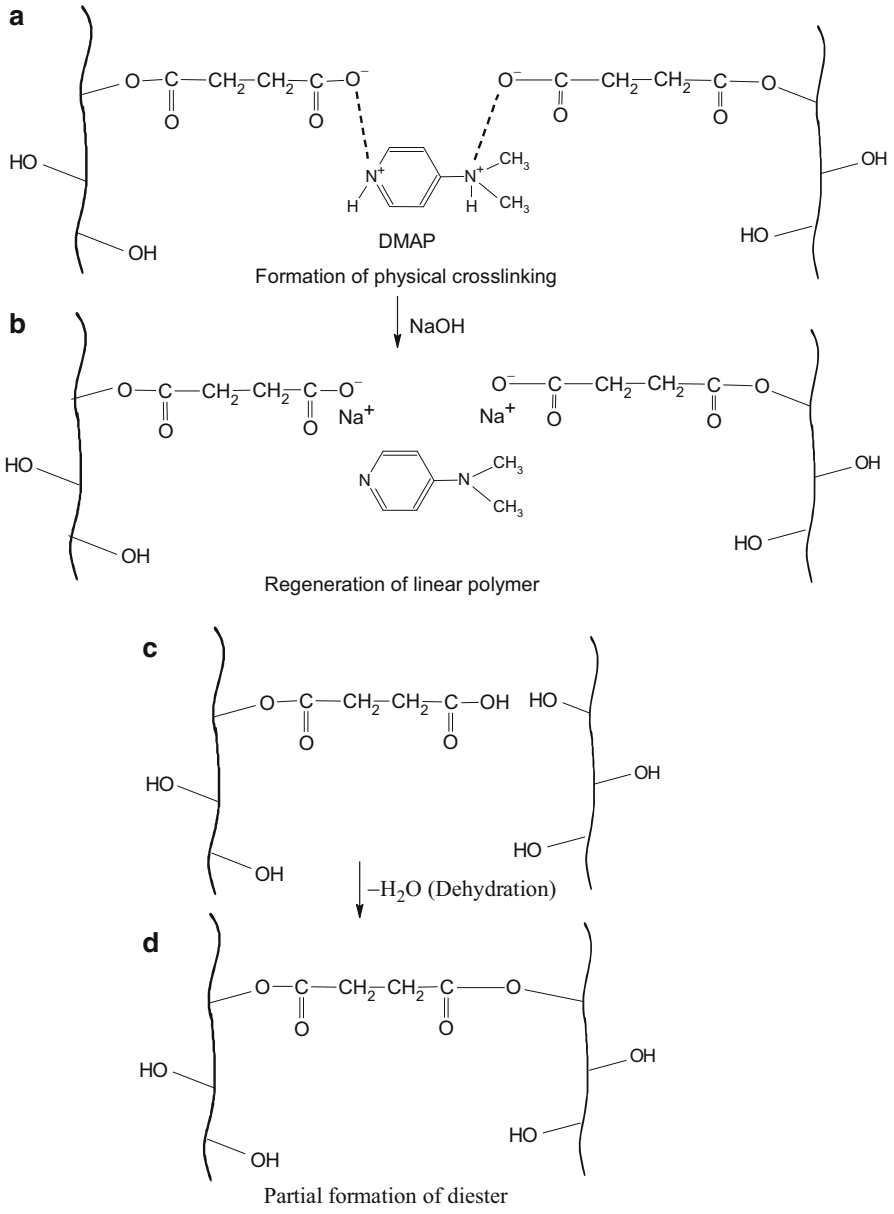


Fig. 16 Synthesis scheme of biodegradable superabsorbent hydrogel

hydrogels were secure and biodegradable materials. The results showed that all of the cellulose/PVA hydrogels exhibited homogeneous porous structures and a certain miscibility. The swelling degree and water uptake of the chemical hydrogels were markedly higher than those of the physical hydrogel (Fig. 18).

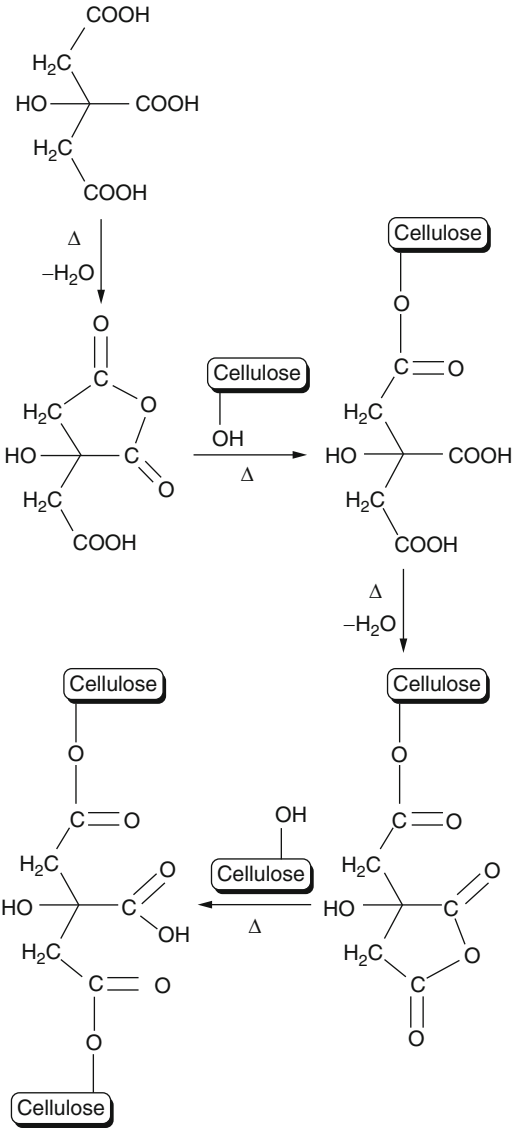


Fig. 17 Crosslinking reaction of cellulose derivatives with citric acid [70]

Fig. 18 Proposed mechanism for crosslinking reaction of ECH with cellulose and PVA

4 Conclusion

The green chemistry approach pushed researches and researchers toward replacing petroleum-based products with natural polymers for environmental concerns. In this respect, polymer networks of crosslinked cellulose derivatives were synthesized to form hydrogels for different purposes starting from sanitary pads and hygienic products to advanced applications such as biomedical field, drug delivery, pharmaceutical ground, and agriculture. In these specific applications, "smart" polymers are required to respond to different environmental changes to induce the required effect. These smart polymers are cheap, adaptable, and biodegradable so that extensive work is continued in order to introduce new generations of these materials to serve in different fields.

5 Future Perspectives

Shortage of fresh water resources is of worldwide concern. Efforts are directed to solve this problem by focusing on hydrogel industry. Hydrogels can be made by chemical modification of natural polymers such as cellulose, carboxymethyl cellulose, starch, guar gum, and so on. They can be used in water holding applications such as retained irrigation. They can be used as vehicles for delivering nutrients and pesticides to the root. Furthermore, they can be applied in wastewater treatment and removal of heavy metals. The new application of hydrogel utilization is in greenhouse industry where they regulate the amount of sunlight that can pass into the shelter and control the water loss.

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Stimuli-Responsive Cellulose-Based Hydrogels

9

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Abstract

Stimuli-responsive hydrogels can spontaneously change their physical and chemical properties in response to changes in the external environment, and they have potential applications in numerous fields as demonstrated in many reports. Cellulose is the most abundant polysaccharide in the natural world, and cellulosic polymers have been considered to be outstanding candidates as building blocks for stimuli-responsive hydrogels with great potential applications for absorption, separation, in the biomedical field, as well as other fields. The main purpose of this chapter is to demonstrate the significance of these materials and provide representative examples regarding the combination of stimuli-responsive hydrogels and cellulosic polymers. Inspired by the merits of both cellulose and stimuli-responsive hydrogels, in this chapter, we will also individually discuss some of the superior properties of stimuli-responsive cellulose-based hydrogels relative to a fossil-based hydrogel, including bulk hydrogels, microgels/nanogels, and injectable hydrogels that respond to stimuli such as heat, pH, ionic strength, light, electric field, magnetic fields, or shear, as well as their major applications. Furthermore, the typical strategies for the preparation of hydrogels (i.e., chemical cross-linking and physical cross-linking), as well as the mechanisms that drive the ability of these hydrogels to respond to various stimuli (i.e., heat, pH, light, special chemicals, electric fields, magnetic fields, and shear), will also be briefly presented in this chapter. This chapter might be useful for the development of novel stimuli-responsive cellulose-based hydrogels with high performance.

Keywords

Stimuli-responsive · Cellulose · Hydrogels · Synthesis · Applications

1 Introduction

Stimuli-responsive behavior is a common phenomenon in the natural world. For example, the living cells in biosomes can change their chemical structures or functions by regulating their assembly behaviors and interfacial properties in order to maintain their biological lives [1]. Actually, many synthetic compounds can also mimic these behaviors, and they can undergo relatively dramatic physical or chemical changes in response to small external changes in the environmental conditions (e.g., temperature, pH, salt concentration, light, electric or magnetic fields, etc.).

Thus, this family of polymers is defined as "stimuli-responsive polymers" [2] (terms such as environmentally sensitive, "smart," or "intelligent" are also used).

A hydrogel (or gel, usually used interchangeably in food and biomaterials fields) is a three-dimensional (or cross-linked) network that is created from a class of synthetic and/or natural polymers [3]. Due to the presence of hydrophilic groups in their polymeric networks, hydrogels can absorb and retain a significant amount of water in aqueous environments [4]. Unlike other cross-linked resins, due to the water-containing network within hydrogels, they are usually soft and exhibit low surface tension that is similar to biological cells. Thus, hydrogels are widely used in drug delivery, for drug control release, for tissue engineering, as wound dressings, and in other fields [5].

The frameworks of stimuli-responsive hydrogels are constructed of stimuli-responsive polymer backbones, which provide the hydrogels with certain features in response to external stimuli. The typical responsive behaviors of hydrogels consist of (1) reversible/irreversible changes of the networks between homogeneous phase and phase separation (or transitions between swollen and collapsed phases) within a short time to change the hydrogels' physicochemical properties, (2) reversible/irreversible changes of the hydrogels' frameworks between cross-linked networks and flexible linear polymers (or sol-gel transitions), and (3) other reversible/irreversible changes in physical properties such as shape, size, optical properties, or dielectric properties. The stimuli responsiveness plays a pivotal role resembling that of a "switch, thus offering us an approach for regulating or controlling the hydrogels' physicochemical properties in various conditions. This switchable behavior provides these materials with numerous applications, such as intra- or extracellular stimuli-triggered drug release [6]; injectable scaffolds for tissue cultures [7]; the recycling of used sorbents for pollutants or water [8], or separation membranes [9]; sensors for minor changes in the surroundings [10]; microfluidics [11]; artificial muscles [12]; and so on.

Cellulose (Fig. 1a) and its derivatives are usually colorless, odorless, and nontoxic solid polymers with other promising merits such as excellent mechanical strength, biocompatibility, high sorption capacities, desirable hydrophilicity,

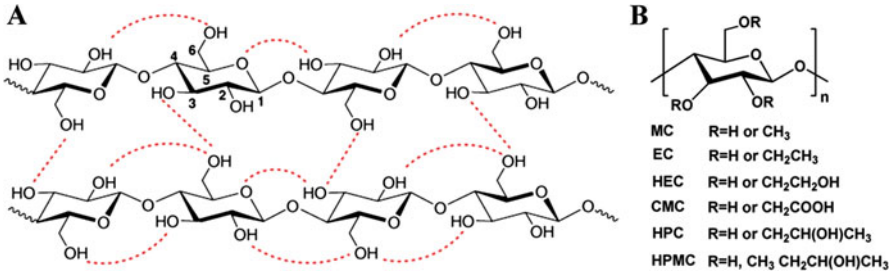

Fig. 1 (**a**) Molecular structure of cellulose illustrating the intermolecular and intramolecular hydrogen bonds [15]. (Copyright 2013 Society of Chemical Industry). (**b**) Structures of some common cellulose derivatives

desirable thermostabilization, and alterable optical appearance [13]. Cellulose can be readily obtained from plants, and this material accounts for one third of the dried weight of plants (PC). Additionally, cellulose can also be synthesized by algae, tunicates, and some bacteria (BC) [14]. The widely reported cellulose derivatives are MC, EC, CMC, HEC, HPC, and HPMC, the structures of which are shown in (Fig. 1b). The conventional applications of these cellulosic polymers have included the preparation of cellulose fibers and papers, and these conventional cellulosic products were usually produced via the viscose process, which consumes a lot of energy and creates pollution [15]. In recent years, stimuli-responsive hydrogels have been demonstrated to be useful and promising materials with potential applications in many fields. Meanwhile, with the rapid development of modern synthetic chemistry, numerous studies have focused on the incorporation of cellulosic polymers or cellulose crystals into stimuli-responsive hydrogels to improve their physicochemical properties. There are three main purposes for the conjunction of cellulosic polymers with stimuli-responsive hydrogels:

1. To Improve the Mechanical Properties
   Desirable mechanical properties are required for a swollen hydrogel, especially if it serves as a scaffold or barrier in the biomedical field. However, a highly swollen hydrogel, created from pure conventional fossil-based polymers such as polyacrylic acid, is always fragile, and it may fracture when it is subjected to an external force [16]. A promising method for improving the mechanical properties of a hydrogel consists of (1) preparing hydrogels with interpenetrating polymer networks (IPN) or semi-IPN structure [17], (2) incorporating other organic or inorganic additives into the hydrogel [18, 19], and (3) designing special structures to release the stress encountered by the network [20]. Cellulose usually serves as the dominant reinforcing phase in plants, and it was widely reported for its ability to serve as an organic additive to enhance the mechanical properties of hydrogels. The molecular structure of cellulose consists of a straight chain composed of β-(1→4)-linked $_{D}$-glucose units. Strong *intramolecular* or *intermolecular* hydrogen bonds exist between the neighboring hydroxyl groups (shown in Fig. 1a), which produce a composite structure bearing coexisting crystallized regions and amorphous regions. For example, the crystallinity of PC is usually in the range from 40% to 60%, but this value is over 60% for BC [21]. In comparison to some irregular fossil-based polymers with good solubility, bulk cellulose or molecular aggregates usually exhibit poor solubility as well as poor dispersity because cellulose molecules have ultrahigh tacticity. However, the native cellulose powder is still able to undergo disassembly and form nanoscale cellulose aggregates such as nanocrystals (with a specific area ~250 m^2/g), nanowhiskers, or nanofibers (with diameters in the range of 5–20 nm) in the presence of an inorganic acid. These cellulose-based nanoaggregates exhibit not only better water dispersity than native cellulose but also excellent mechanical performance due to their crystalline structure [22]. For example, the tensile strength of a cellulose nanofiber is over 7500 MPa, and its Young's modulus usually reached up to 140 GPa [23]. These cellulose-based

nano-aggregates are extraordinarily promising for their ability to improve the mechanical properties of hydrogels.

2. To Improve the Biocompatibility and Biodegradability
   Generally, hydrogels are considered as biocompatible materials. The undesirable allergies and inflammation caused by hydrogel implants can be effectively prevented because the adhesion of immunocyte or protein antibodies onto the surfaces of hydrogels can be avoided due to the excellent hydrophilicity and low surface tension of these materials. The incorporation of other biocompatible components into hydrogels can serve to inhibit undesirable stimulation caused by hydrogel implants. The cell viability results described in recent reports demonstrated that the biocompatibility of hydrogels can be effectively enhanced via the incorporation of cellulosic polymers [24, 25]. On the other hand, the biodegradability is also important because biodegradable hydrogels can be spontaneously decomposed into smaller molecules in physiological environments and thus easily excreted via sweat or urine instead of requiring removal by surgery, which may cause unnecessary tissue damage. It should be noted that the by-products produced from these degradation processes should be nontoxic to both humans and the natural environment. Generally, the degradation of fossil-based polymers only occurs under extreme conditions (i.e., intense heat or UV irradiation). The by-products that accompany the degradation process, such as organic acids, aldehydes, or alcohols, may be toxic to humans. In contrast, cellulosic polymers, in the presence of cellulase, can be rapidly decomposed into nontoxic glucose-based molecules under mild conditions. However, cellulose-based hydrogels cannot be digested or metabolized by the human body because it does not synthesize cellulase. The degradation of cellulosic polymers can only be effectively controlled by cellulase. Some researches have demonstrated that the degradation of cellulose-based hydrogels usually requires over 60 weeks to take place when they are exposed to physiological conditions [26]. Thus, cellulose-based hydrogels can be considered to be biodurable and can be used as biodegradation-controlled materials that are suitable for long-term service, as is the case with other fossil-based hydrogels.
3. To Decrease the Production Cost
   Fossil fuels have been considered as important strategic resources for many countries, particularly in recent years. The procedures for the mining, machining, and synthesis of fossil-based materials are usually cost-intensive and have large environmental footprints. The search for novel carbon resources is a critical issue for the sustainable development of human society [15, 27]. Cellulose, which is mainly generated by plants and organisms in nature at a scale of 1.5×10^{12} tons per year, is the most abundant renewable resource. However, in recent years, most of the cellulose produced was decomposed to CO_2 via metabolism of bacteria and fungi that exist in the air, water, and soil. Only 0.2% of cellulose was used for the industrial fabrication of materials such as paper and textiles [15]. The development and application of biomass materials has become increasingly important as researchers seek to reduce industrial costs and environmental risks.

4. Others
   As is the case with synthetic polymers, some cellulose derivatives can also reversely regulate their conformations under external stimuli. For example, MC, HPC, and HPMC exhibit thermo-responsive behavior resembling that of PNIPAAm and PEO-*b*-PPO-*b*-PEO (or Pluronic® F-127) [28–30]. Meanwhile, CMC exhibits well-defined pH-responsive behavior resembling that of polyacrylic acid (PAA). These cellulosic polymers with native responsive behaviors provide outstanding candidates as precursors for stimuli-responsive hydrogels. Furthermore, the backbones of cellulosic polymers usually contact active groups, such as hydroxyl groups in the HPC component and carboxyl groups in the CMC component. These active groups can not only react with cross-linking reagents to form a network, but they can also be modified with other pendent functional groups.

In this chapter, we will briefly introduce the general gelation strategies in Sect. 2 and the basic theories regarding stimuli-responsive behavior in Sect. 3. These discussions may be useful for improving the performance of cellulose-based hydrogels exhibiting with classic responsibility such as thermo- and pH-responsibility, and they may also provide some insight regarding the preparation of cellulose-based hydrogels with novel responsiveness to stimuli such as light, as well as electric and magnetic fields. In Sect. 4, great attention will be paid to the properties and applications of cellulose-based stimuli-responsive hydrogels with different responsive behaviors, with particular focus devoted to the significance of employing cellulosic polymers in stimuli-responsive hydrogels. Some relevant examples from the literature will also be briefly introduced in this section.

2 Classification of Gelation

Gelation (or a sol-gel transition) can be defined as the process through which a solubilized polymer with free macromolecular chains undergoes a collapse to a poorly dispersed network with contractive macromolecular chains. In this process, a solution of free macromolecular chains can be defined as a "sol," and a network of contracted and interconnected macromolecular chains can be defined as a "gel." The critical point of a sol-gel transition is defined as the "gel point" [31]. The hydrogels can be classified as physical gels or chemical gels according to the manner by which two neighboring polymer chains are linked.

2.1 Physical Gelation

Physical gelation is a "sol-gel" process, and it is usually triggered by the formation of temporary associations between free polymer chains. These associations can include the entanglement of coiled polymer chains, electrostatic forces between ionized groups or metal ions, the formation of crystallites between two or more polymer

chains, hydrogen bonding, clathration, aggregation due to the hydrophobic effect, and so on. Physical gelation is usually reversible because these temporary associations will dissipate when the hydrogels are exposed to external stimuli such as changes in the temperature, pH, ionic strength, solvent polarity, or stress. For example, the clear solutions of MC, HPC, and HPMC will spontaneously be converted into cloudy gels when they are subjected to an elevated external temperature. When the heat is removed, the cloudy gel will revert back to a clear solution [28–30]. The mixture of CMC and polyvinylamine can form an electrolyte hydrogel via electrostatic interactions between $-COO^-$ and $-NH_3^+$ at a certain pH value, and the electrostatic interactions can be disrupted via increasing the concentration of NaCl [32]. The cage-like macrocycle cyclodextrin, with its hydrophobic cavity, can serve as a supramolecular host to entrap hydrophobic guest molecules to form inclusion complexes, and this complexation behavior can be used to link the two polymers together via the threading of the polymer chains as guests through the macrocyclic host molecules. However, the linkage points can also be weakened via the addition of other guest molecules that have stronger binding affinities with these hosts [33].

2.2 Chemical Gelation

Chemical gelation is triggered via the formation of strong and stable covalent bonds, and this bond formation is usually irreversible unless they are subjected to extreme conditions or catalysts are added that facilitate the cleavage of these bonds. In order to form robust covalent bonds, di- or multifunctional molecules, aggregates of molecules, are usually incorporated as the cross-linking reagents to link the neighboring free polymer chains bearing active groups via the reactions between functional molecules and cross-linking reagents. The cross-linking processes are usually effectively achieved with the promotion of light, heat, catalysis, or radiation. The chemical reactions that are usually employed to cross-link polymers include radical polymerization between vinyl groups [34], condensation between amine and carboxyl groups [35], ring-opening reactions between epoxy and amine or carboxyl [36], coupling between two of thiol groups [37], Schiff's base reactions between glutaraldehyde and amine [38], click chemistry between azides and alkynes [39], or thiol-ene and other relevant reactions [40].

3 Responsive Mechanisms

3.1 Thermo-Responsiveness

Thermo-responsiveness can be defined as a spontaneous and reversible phase separation process that a polymer solution undergoes across a specific temperature value without any cleavage of covalent bonds. This particular temperature is defined as the "cloud point." Generally, under a constant pressure, it is not a fixed value because it

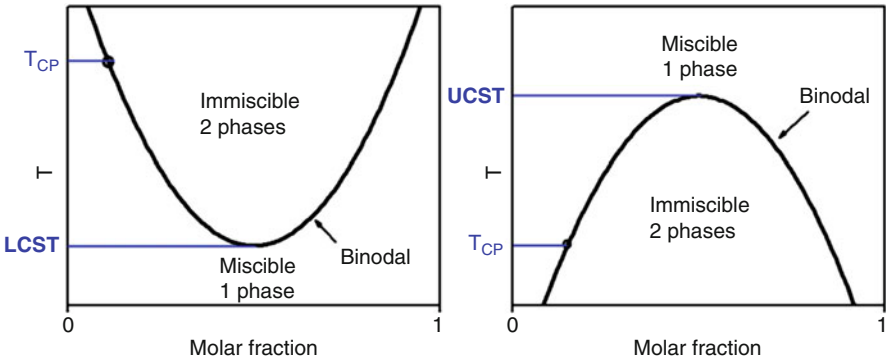

Fig. 2 Phase diagram for a polymer solution depicting an LCST (left) or UCST (right) [42]. (Copyright 2015 Elsevier Ltd)

mainly depends on the concentration of the polymer solution as well as other factors including the polymer's chemical structure, the ratio between the hydrophilic and the hydrophobic components of the polymer, the nature of the polymer and its molecular weight, or doses of additives in the polymer solution [41–43]. The lowest and the highest cloud points are, respectively, defined as the lower critical solution temperature (LCST) and the upper critical solution temperature (UCST, shown in Fig. 2). If the temperature of a polymer solution crosses the coexistence curve, the polymer solution consisting of one homogeneous phase will convert to a mixture composed of two miscible phases (often called "miscible-immiscible"). The most significant difference between the LCST and the UCST is the relative strength of the solvent effect and intermolecular interactions. The solvation that occurs between solvent molecules and polar groups in polymer backbones facilitates the dissolution of polymer chains, whereas the intermolecular interactions, such as hydrogen bonds or electrostatic interactions, facilitate the aggregation and precipitation of polymer chains.

3.1.1 LCST

LCST polymers are soluble when the external temperature is lower than their cloud point temperature (T_{cp}), while they are insoluble when the surrounding temperature is higher than T_{cp}. This behavior ascribes to the competition between solvent effect and intermolecular interactions. For example, PNIPAAm is the most famous LCST polymer that undergoes a phase transition at ~32 °C because the highly polar -NH- groups as well as the nonpolar -$CH(CH_3)_2$ groups both coexist in the backbone of PNIPAAm [44]. When the external temperature is below 32 °C, the solvation between water molecules and -NH- groups (or hydration in this case) is dominant, which overcomes the hydrophobic effect taking place on account of the -$CH(CH_3)_2$ groups. On the contrary, when the external temperature is above 32 °C, the hydration is weakened, and the hydrophobic effect is dominant; thus PNIPAAm chains tend to aggregate and form precipitates. In addition to PNIPAAm, some other synthetic

polymers also exhibit the LCST thermo-responsive behavior in pure water, such as PNVA derivatives [45], PVME [46], PNVCL [47], copolymer such as Pluronic® F-127 [48], etc.

3.1.2 UCST

In contrast with LCST polymers, UCST polymers are soluble when the external temperature is above their T_{cp}, while they are insoluble when the temperature is below their T_{cp}. When the external temperature is lower than the polymer's phase transition temperature, the dissolution of the polymer is inhibited because the *inter*- and *intra*molecular forces of UCST polymers are usually much stronger than those of LCST polymers. When the external temperature is higher than the polymer's phase transition temperature, the dissolution of the polymer is promoted because the molecular forces between the polymer chains are weakened, thus providing water molecules with an opportunity to interact with polar groups in the polymer chains. Generally, the UCST behavior can be regulated via alternatively changing the amount of polar groups on the polymer chains or by changing the molecular weight of the polymer. Only a few of polymers exhibit UCST behavior in water at temperatures in the range from 0 °C to 100 °C. Some representative UCST polymers, such as PNAGA [49], PDMAPS [50], PSPP [51], and PMAAm [52], all possess highly polar zwitterionic groups, which can help generate strong intermolecular interactions.

3.2 pH or Ionic Strength Responsiveness

Due to the existence of ionizable pendant groups or electrostatic groups in polymer chains, the "stretch-coil" behavior of a pH-responsive polymer mainly depends on the electrostatic interactions within the polymer chain or with other polymer chains. In the solution with an initial pH, the ionizable groups will not gain or lose protons; thus there are no electrostatic interactions between the polymer chains (possibly only hydrogen bonds exist). When the pH is changed, the polymer's dissolution in aqueous solution is promoted because protons will dissociate from, or absorb onto, the ionizable groups in the polymer chains. The resultant charges will enhance the polarity of the polymer chains, thus promoting the attachment of water molecules onto the charged groups to form hydrated ions. Meanwhile, the electrostatic repulsion also prevents the neighboring polymer chains from coming into contact with each other. In the case of a pH-responsive hydrogel, its swelling ratio will be further enhanced because the charged groups induce more water molecules to diffuse into the hydrogel's network to balance the difference in the osmotic pressure between the exterior and the interior of the hydrogel.

Hydrogels that exhibit ionic strength responsiveness usually also exhibit pH responsiveness. The hydrogel's swelling ratio will decrease when the ionic strength is increased. This behavior can be attributed to the following factors: First, the charged groups on the hydrogel's backbones will be partly screened by the counterions in water, and the electrostatic repulsion between the neighboring polymer

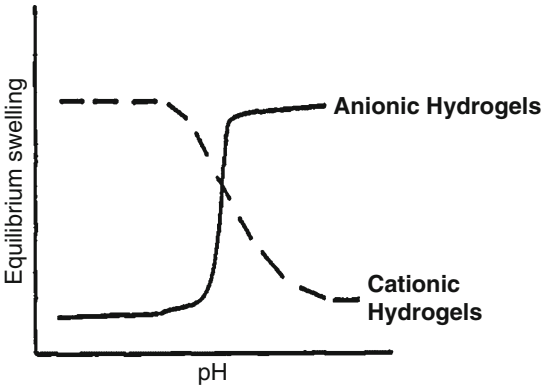

Fig. 3 Equilibrium swelling behaviors of anionic and cationic hydrogels. These behaviors are influenced by the ionic pendant groups. (Reprinted with permission from Khare et al. [53]. Copyright 2015 Elsevier B. V)

backbones is weakened. Second, increasing the ionic strength of the external solution will heighten the difference in osmotic pressure between the exterior and interior of the hydrogel, thus causing the water molecules within the hydrogel to migrate to the external solution to balance the osmotic pressures.

3.2.1 Anionic Responsiveness

Anionic polymers are hydrophilic when the pH value of the surrounding solution is higher than their pK_a. PAA, as a typical pH-responsive polymer with a pK_a of ~4.6, exhibits poor solubility in aqueous solution with a pH value that is below its pK_a. In this case, the *inter*- or *intramolecular* hydrogen bonds between neighboring PAA chains create the curled and aggregative conformation of the polymer chains. When the pH is above 4.6, carboxyl groups will gradually lose protons to form anionic carboxylates, which have better water-binding capabilities. The electrostatic repulsion between neighboring polymer chains also promotes the dissolution of PAA. Therefore, a PAA-based hydrogel will absorb water in an alkaline solution while releasing water in an acidic solution (shown by the dashed line in Fig. 3). However, it should be noted that the ionic strength responsiveness of a PAA-based hydrogel cannot be ignored especially in extremely alkaline solutions because a large number of cations, such as Na^+, may shield the carboxylate groups, which will restrain the water-absorbing capabilities of the hydrogel [54]. CMC is the most representative pH-responsive cellulosic polymer because its backbone contains many pendent anionic carboxylate groups as is the case with PAA. The hydrogels thereof exhibit both pH- and ion strength-responsive behaviors. In addition, various functional groups can be grafted onto CMC backbones due to the reactive nature of carboxyl groups.

3.2.2 Cationic Responsiveness

Cationic polymers exhibit good solubility in water when the pH value of the external environment is lower than the polymers' pK_a. PDMAEMA is a typical cationic polymer with a pK_a of 7.0–7.3 in aqueous solution [55] (in fact, PDMAEMA is a dual responsive polymer exhibiting both pH and thermo-responsiveness with an

LCST of ~31 °C [56]). When the external pH is lower than this range, the lone pair electrons in the sp^3 orbitals of the nitrogen atoms will accept protons to form $-NH_4^+$, which enhances the hydrophilicity of PDMAEMA. Thus, hydrogels that are based on cationic polymers will swell at low pH values and collapse at high pH values (shown by the solid line in Fig. 3). Besides PDMAEMA, other cationic polymers, such as PDEAEMA [57] and PAAm [5], also exhibit pH-responsive behavior.

3.3 Photo-Responsiveness

Light is much more readily manipulated than other stimuli such as temperature or pH. The incorporation of functional groups that were capable of absorbing light and transferring light to heat and thus trigger the thermo-responsive behavior of these hydrogels was reported during the preparation of the earliest photo-responsive hydrogels in 1990 [58]. However, the responsiveness was weak because this process required the conversion of "light to heat" that was thus accompanied by an elevated temperature. For pH- and/or thermo-responsive hydrogels, their responsive behaviors only depend on the physical changes within their frameworks. However, most photo-responsive hydrogels can change their physicochemical properties via photochemical reactions within their frameworks, and new chemical compounds are produced through this process. The rate at which a hydrogel responds to light stimuli is determined by the kinetics of the photochemical reaction, which relates to the reaction temperature or concentrations of the reactants/products, essentially absorbed intensity (I_{abs}), and overall quantum yield (φ). The prior parameter is primarily determined by the wavelength, concentrations of the reactants (as it is only effective at high concentrations), and the depth of light penetration. The latter parameter depends on the efficiency of the reaction and the fluorescent quenching effect of both the reactants and products. Photochemical reactions with high I_{abs} and φ facilitate rapid response rates and remarkable changes in the physicochemical properties.

3.3.1 Isomeric Responsiveness

Isomeric reactions are one of the most widely used physicochemical reactions for preparing hydrogels with photo-responsive properties. Among these reactions, the monomolecular *cis-trans* shift of azobenzene is the most representative isomeric reaction. Azobenzene can undergo a *trans*-to-*cis* transition at 360 nm, and the inverse transition takes place under light irradiation at a wavelength of 440 nm. It has been reported that azobenzene molecules existing as *cis* species are hydrophilic, whereas their *trans* forms are hydrophobic [59]. Furthermore, the stacking sequences between neighboring azobenzene molecules vary for azobenzene molecules with different forms because their *trans* isomers are positioned in the same plane with a length of 9 Å and their *cis* isomers are three-dimensional structures with a length of 5.5 Å (Fig. 4) [59, 60]. Azobenzene has frequently been incorporated into photo-responsive hydrogels and serves a critical role in the cross-linking process with neighboring polymer chains via the formation of supramolecular inclusion

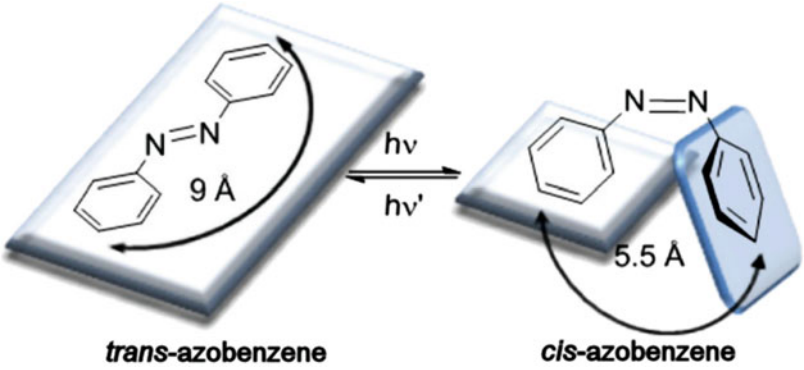

Fig. 4 Photoisomerization of azobenzene [59]. (Copyright 2012 Merino and Ribagorda; licensee Beilstein-Institut)

complexes with other cage-like molecules [61]. In addition, the light wavelength that triggers the conformation transition can be regulated via chemical modifications of the azobenzene molecules. Cyclization is another common isomeric reaction. For example, non-cyclized spirobenzopyran is a linear molecule bearing zwitterionic groups, which render it hydrophilic. However, upon exposure to light radiation, spirobenzopyran will be converted into a hydrophobic polymer because the self-cyclization takes place and the zwitterionic groups are consumed [62].

3.3.2 Covalent Responsiveness

The cleavage of covalent bonds within molecules usually leads to covalent-responsive behavior. In this responsive process, two new compounds will be created due to the cleavage of a covalent bond, or a new dimer will be created due to the formation of new covalent bonds. For example, a polymer containing *o*-methoxy nitrobenzene moieties can readily degrade into an oligomer when it is exposed to light irradiation at 350 or 750 nm [63]. In contrast, molecules containing coumarin or anthracene groups can form dimers via a reversible Diels-Alder reaction. These molecules can serve as cross-linkers to form chemical hydrogels [64, 65]. These reversible cross-linking processes may facilitate the preparation of injectable hydrogels capable of reversible "sol-gel" transition behavior.

3.4 Chemical Responsiveness

Chemical-responsive hydrogels can be defined as the hydrogels that can regulate their swelling properties or undergo a "sol-gel" transition in the presence of target molecules that act as triggers. The responsive mechanism may involve (1) binding of target molecules bearing particular functional groups onto the hydrogel's backbones, (2) the cleavage of covalent bonds caused by the incorporation of target molecules

(such as enzymes), and (3) the changes in the pH or temperature caused by a reaction between the target molecules.

3.4.1 Glucose Responsiveness

The glucose-responsive behavior proceeds via three mechanisms [66]. The first mechanism is based on the pH change that is induced by the decomposition of glucose in the presence of glucose oxidase (GOx). Glucose molecules diffuse from the external solution into the hydrogel's network and subsequently are converted into gluconic acids via reactions catalyzed by GOx. Thus, the phase transition behavior of the hydrogel is motivated due to the changes in the pH value in the presence of gluconic acids (the reaction shown in Fig. 5a). The second mechanism is based on the degradation of hydrogels due to the binding between glucose and

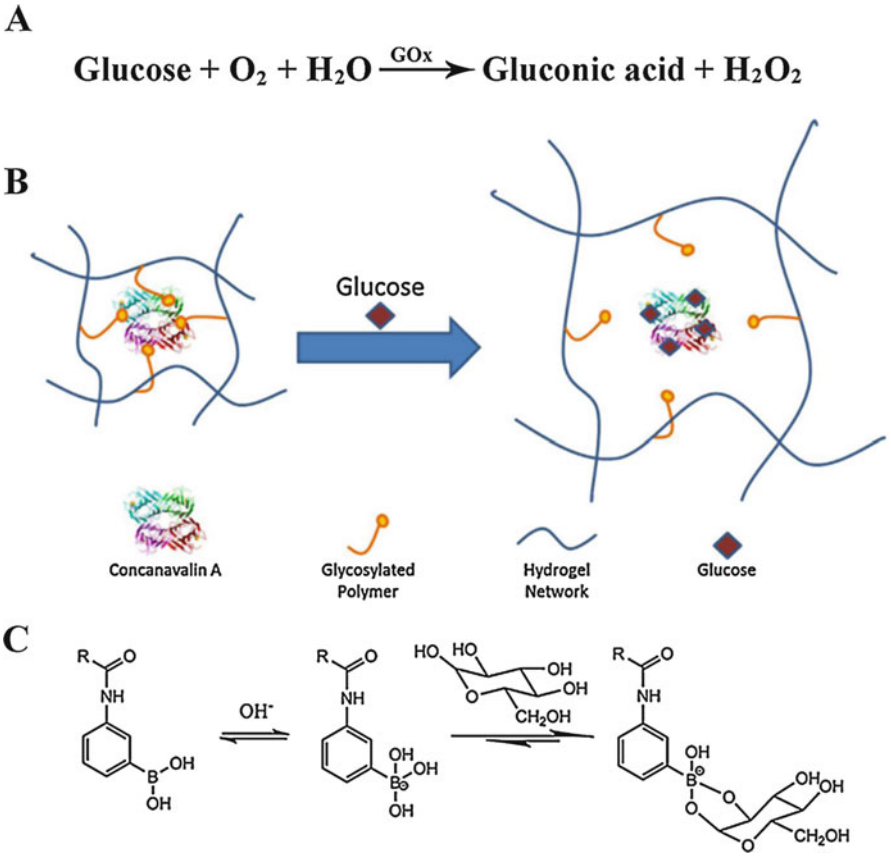

Fig. 5 (**a**) The reaction between glucose and oxygen catalyzed by GOx. (**b**) Illustration of the swelling mechanism of Con A-based glucose-responsive hydrogel. (**c**) Reaction between glucose and PBA [5]. (Copyright 2015 Elsevier B. V)

concanavalin A (Con A). The polymers bearing glycosylated backbones can bind with the neighboring polymers bearing Con A to form a cross-linked network due to the binding of the glycosyl moieties with Con A. However, the binding affinity between Con A and glucose molecules in external solution is higher than that between Con A and glycosyl moieties. Therefore, the binding between the glycosyl units and Con A will be disrupted, and the hydrogel subsequently undergoes a "gel-sol transition (as shown in Fig. 5b). The third mechanism is based on the changes in the charges caused by the binding of glucose with PBA. The PBA moieties on the backbones will bind with glucose to form cationic boron products (the reaction is shown in Fig. 5c) that increase the charge density within the hydrogel, resulting in the swelling of hydrogels.

3.4.2 Enzyme Responsiveness

Enzyme-responsive behavior can be understood as enzymatic decomposition. The enzyme-responsive hydrogels are cross-linked by peptide chains, and their peptide sequences can be recognized and subsequently digested by a specific enzyme, ultimately leading to the degradation of the hydrogels.

3.4.3 Alcohol Responsiveness

Some polymers, such as PNIPAAm, exhibit critical soluble behavior in mixtures of ethanol and water. This ethanol-responsive behavior is primarily determined by the concentration of ethanol. PNIPAAm has both lower and upper critical ethanol-responsive concentrations (usually, respectively, denoted as C_{E1} and C_{E2}), which are 16.7 and 51.9 vol.% in aqueous solutions at 25 °C (shown in Fig. 6). If the ethanol concentration is lower than 16.7 vol.%, the limited ethanol molecules are unable to disrupt the hydrogen bonds between water and -NH- groups in the PNIPAAm backbones. In this case, PNIPAAM is highly soluble in the aqueous ethanol solution. With an increasing ethanol concentration, the hydrogen bonds between water and the -NH- groups are gradually destroyed by ethanol molecules, and PNIPAAm undergoes a "coil-to-aggregate" phase transition. When the ethanol

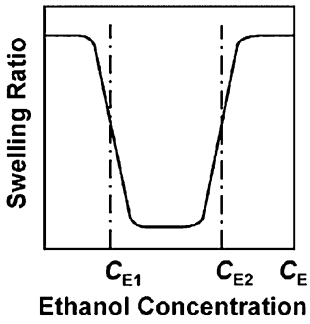

Fig. 6 Ethanol-responsive behavior of PNIPAM [67]. (Copyright 2012 American Chemical Society)

concentration is higher than C_{E2}, the -NH- groups effectively combine with ethanol molecules, thus causing the redissolution of PNIPAAm [67].

3.5 Electric Field Responsiveness

Electrolyte-based hydrogels usually respond to electric fields due to the fixed charges within their network structures. The responsive mechanism can easily be understood by considering sodium polyacrylate hydrogel as an example. In the absence of an electric field, the overall hydrogel is electroneutral. In this scenario the Na^+ ions with their positive charges act as counterions to the $-COO^-$ moieties and are partly bound with these groups via electrostatic interactions. Some Na^+ ions are also well-dispersed in water within the hydrogel's network. When an external electric field is applied to the hydrogel, the Na^+ ions begin to migrate toward the cathode, which results in an ionic gradient along the direction of the electric field, whereas the $-COO^-$ units migrate toward the anode because their motions are restrained by the cross-linked backbones of the hydrogel. Consequently, ion concentrations inside and outside of the gel are different. This difference between ionic concentrations creates an osmotic pressure difference between the anode- and cathode-facing sides of the hydrogel [68]. For anionic sodium polyacrylate hydrogel, the osmotic pressure on the anode-facing side is higher than that encountered on the cathode-facing side. In this case, water molecules tend to migrate from the cathode side to the anode side, which induces swelling of the hydrogel on the anode-facing side and shrinkage on the cathode-facing side. The opposite swelling/shrinking behavior in one region of the hydrogel thereby causes the overall structure of the hydrogel to become deformed. It should be noted that the electrolyte hydrogels only exhibit electric field-responsive behavior in a special pH range because the charged groups may be neutralized when the pH is changed. For example, hydrogels of sodium polyacrylate would lose their electric responsibility upon exposure to a strongly acidic environment [69].

3.6 Shear Responsiveness

Shear-responsive hydrogels can reversibly change their viscosity when an external shearing force is applied or removed. The shear-responsive behaviors can be classified as either shear thinning or shear thickening. In the case of shear thinning, temporary interactions that link the neighboring polymer chains together within a hydrogel, such as hydrogen bonds or electrostatic interactions, are unstable and can be provisionally destroyed by the application of a shear force. Thus the hydrogel will exhibit a reversible "gel-to-sol" phase transition [70]. In contrast, the latter case usually takes place in hydrogels which contain inorganic micro−/nanoparticles as part of their composition. The polymer chains binding with solvent molecules serve as dispersants to prevent the aggregation of micro−/nanoparticles.

Once the external shearing force is applied, the polymer chains are extruded out from the space between neighboring particles, and the hydrogel assumes a solid-like status [71].

3.7 Magnetic Responsiveness

Magnetic hydrogels are usually prepared via entrapping magnetic micro-/nanoparticles (such as γ-Fe_2O_3, Fe_3O_4, or $CoFe_2O_4$ nanoparticles) into the cross-linked networks [72]. For the bulk magnetic hydrogels that are exposed to an external magnetic field, the entrapped magnetic particles can change the distribution of the hydrogel's backbones, which will alter the properties of the hydrogel, such as the size, shape, or other physiochemical properties [73, 74]. In contrast with the hydrogel's polymer chains, the magnetic micro-/nanogels can migrate along the direction of the external magnetic field. However, strictly speaking, the migration of magnetic micro-/nanogels cannot be designated as typical magnetic-responsive behavior because the physiochemical properties of an individual particle are not changed during the magnetic migration. However, the external magnetic field may create other physical stimuli such as heat, which provide promising potential in thermal cancer treatment and targeted drug release.

4 Properties and Applications of Stimuli-Responsive Cellulose-Based Hydrogels

4.1 Thermo-responsive Cellulose-Based Hydrogels

4.1.1 Wound Dressings

Wound infection can often cause an injury to become more severe, increasing the risk of amputation and death [75]. Keeping a wound moist is a critical factor in allowing a wound to heal because moist conditions facilitate tissue restoration and limits the propagation of microorganisms. Additionally, these conditions can alleviate pain [76]. The ideal wound dressings should (1) adhere onto the surface of a wound for sufficient time without leading to abscission, (2) absorb the excess tissue fluid that exudes from the wound, (3) ensure the wound remains moist, (4) facilitate the transport of gas molecules, (5) protect the wound against heat, (6) readily detach from the wound when needed without inducing pain [77], and (7) have enough mechanical strength to avoid undesirable fracture in normal daily activities.

Physical hydrogels with appropriate LCSTs are considered to be the excellent candidates as wound dressings. First, polymer solutions that are initially at room temperature will undergo a "sol-gel" transition once they contact the surface of a wound with a higher temperature (such as 37 °C, which is encountered under physiological conditions). Subsequently, the polymer chains regulate their conformation to form a physically cross-linked hydrogel that covers the wound. Second, the hydrogels contain water molecules in their networks and can thus keep the

wound moist, while the excess tissue fluid from the wound can also be absorbed by the hydrogels. In addition, due to the continuous or semicontinuous pore structure that exists within hydrogel, gas molecules can freely pass through the hydrogel layer. Third, the hydrogel dressings can be easily removed in a pain-free manner via local cooling such as exposure to cold water when their removal is desired.

The incorporation of cellulosic polymers to the hydrogel's network is a promising method for preparing versatile and robust wound dressings. Firstly, cellulosic polymers contain numerous hydroxyl groups on their backbones, which facilitate the mucoadhesion of a hydrogel with epithelial tissue, because temporary interactions, such as electrostatic interactions, van der Waals forces, or hydrophobic effect, will occur between polar groups in the backbones of cellulosic polymers and the epithelial layer [78].

In addition, the mucoadhesion can be further enhanced by modifying the hydroxyl groups with other polar groups or polymer chains. Secondly, some cellulosic polymers, such as HPC, HPMC, and MC, exhibit distinct thermo-responsive behavior, which can be directly used as the matrix of a thermo-responsive hydrogel for a wound dressing. Meanwhile, the hydrogel's LCST can be regulated by changing the polymer's structure to satisfy a given requirement. Thirdly, the polar groups on cellulosic polymers facilitate the formation of a composite hydrogel bearing other polymers or small molecules such as antibiotics [79] or chitosan [80], which can inhibit the propagation of bacteria on the surface of a wound. Fourthly, some cellulosic polymers, such as CMC, can form weak electrostatic interactions with other charged components to enhance the hydrogel's mechanical properties. In addition, it is notable that BC-based hydrogel wound dressings have been demonstrated to have been shown to promote wound healing, possibly due to their distinctive 3D structure that resembles normal skin tissue [81].

4.1.2 Vaginal Drug Release

As of 2016, over 12 million people have died from acquired immune deficiency syndrome (AIDS) globally, and over 39.6 million people were infected by human immunodeficiency virus (HIV). Therefore, HIV infection poses a significant threat to global public security [82]. Sexual behavior is one of the critical routes for HIV transmission, especially from males to females. It has been verified that the risk of infection of women is eight times higher than men due to the physiological structure of the vagina [83].

Sustained drug release in the vagina is an effective method for preventing HIV infection. The ideal vaginal drug delivery platforms are expected to have the following properties: (1) excellent adhesion onto epithelial cells to avoid the unexpected leakage with the washing of vaginal fluid, (2) excellent biocompatibility and nontoxicity, and (3) facile private implantation.

Cellulose-based thermo-responsive injectable hydrogels are considered to be excellent carriers for anti-HIV drugs (generally, for vaginal drug release, pH responsiveness is also required as will be discussed in Sect. 4.2.2). First, injectable hydrogels can be easily injected into the vagina by the patient, and they usually undergo a "sol-gel" transition when they encounter the external conditions at the

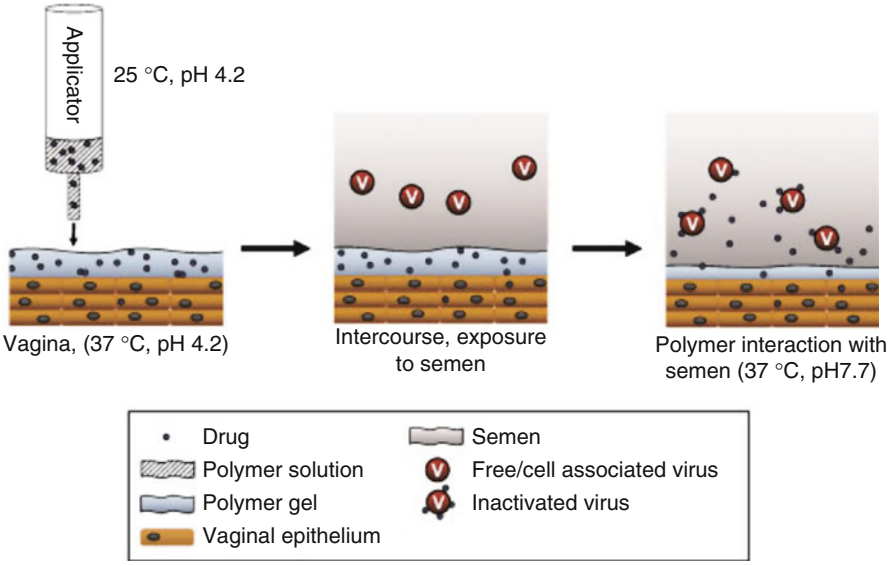

Fig. 7 Schematic depiction of the behavior of an LCST injectable hydrogel in response to the temperature and pH stimuli during vaginal drug release. Upon exposure to semen, the gel loses its mechanical properties and is converted to a liquid again, thereby releasing the entrapped drugs [87]. (Copyright 2006 Wiley-Liss, Inc. and the American Pharmacists Association)

injection site (shown in Fig. 7). Second, the fluid polymer solution will form a physically cross-linked gel and cover the epithelium because the temperature of the vagina is higher than room temperature. Meanwhile, as is the case with wound dressing hydrogels, the polar groups in the cellulosic polymers will facilitate mucoadhesion between the hydrogel and the tissue. Third, cellulosic polymers have been demonstrated to be nontoxic and biocompatible; thus some undesirable symptoms after the implantation procedure can be avoided. Thermo-responsive cellulosic polymers are suitable for use not only independently as drug carriers [84] but also in combination with other biocompatible polymers such as Pluronic® copolymers, to form composite hydrogel with better biocompatibility and mucoadhesion [85, 86].

4.1.3 Tissue Culture

The complete and effective repair of damaged tissues and organs is the ultimate aim of surgical operations. Usually there are two approaches that are employed to achieve this aim. One strategy is to completely replace the damaged tissues with synthetic materials. The other approach is to guide the histiocytes to propagate along with a predesigned shape and size via employing a synthetic scaffold [88]. The ideal scaffold materials are expected to exhibit the following properties:

1. Nontoxicity and biodegradability. The scaffold can be decomposed in a physiological environment when the damaged areas are adequately covered by regenerative histiocyte.

2. A continuous or semicontinuous porous structure, which serves as a passageway for the transport of metabolic wastes and nutrients.
3. Desirable surface physicochemical properties capable of facilitating the histiocyte propagation.
4. Readily machined into a particular shape or can mimic the natural texture of normal tissues.
5. Desirable mechanical properties that withstand normal daily activities [89].

Cellulose-based hydrogels with sol-gel transition behavior can provide suitable platforms for tissue cultures. First, cellulosic polymers have been widely used in tissue engineering due to their excellent biocompatibility and nontoxicity. Thermo-responsive polymers such as HPC, HPMC, or MC can serve as the matrices of hydrogel scaffolds. Polymer solutions can be selectively injected into an injured tissue at room temperature via a minimally invasive surgical operation. In response to the higher temperature encountered within the human body, the polymer solution will be converted to a gel and become deposited on the damaged tissue [90]. In addition, the polymer sols can also be pre-machined into a solid scaffold with various shapes using a mold. Second, the porous structure of the physical hydrogel facilitates the interchange of wastes and nutrients. Meanwhile, the pore size can be regulated by adding different amounts of pore-forming agents or adjusting the cross-linking degree. Third, the mechanical properties of the hydrogel scaffolds can also be regulated via (1) changing the cross-linking degree, (2) changing the concentration of the cellulosic polymer solutions, or (3) adding other components with better mechanical performance. Fourth, unlike crystalline native cellulose, mono cellulosic polymer chains can also partially degrade in less than 12 weeks in the absence of cellulase [91]. Fifth, the incorporation of nanofabricated cellulose and CNC can remarkably enhance the scaffold's mechanical properties due to their high crystallinity.

4.1.4 UCST Hydrogels

Cellulose-based hydrogels with LCST behavior have been widely used in various fields. However, the hydrogels with UCST properties also have some promising applications. In protein separation, for example, UCST polymers that form gels at elevated temperatures can capture proteins and release these proteins at low temperature because the UCST polymers undergo "gel-sol" transitions at low temperatures (shown in Fig. 8) [92]. UCST hydrogels can also be used in drug release. For example, drugs can be entrapped within the hydrogel at normal body temperature and freely diffused out from the hydrogel when the patient experiences a fever because the hydrogel networks become swollen at elevated temperatures [93]. Similarly, in tissue culture, a tissue sample can readily detach from a UCST physical hydrogel coating because the UCST polymers undergo a rapid "gel-to-sol" transition when the external temperature is slightly changed [94]. With the development of synthetic technologies, a growing variety of UCST polymers provide promising potential as cellulose-based hydrogels with advanced biomedical applications.

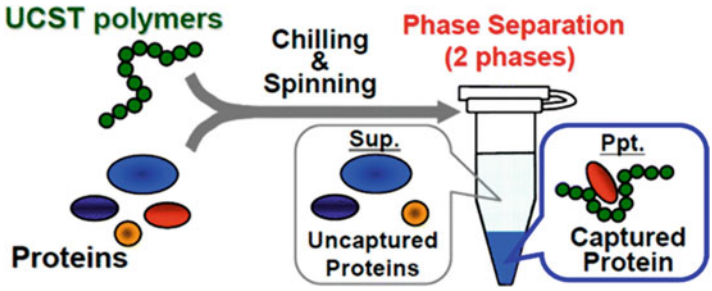

Fig. 8 Illustration depicting the use of UCST polymers for protein separation. The captured protein can be precipitated and collected, while the uncaptured proteins remaining in the solution are discarded [92]. (Copyright 2013 American Chemical Society)

Table 1 Locations within the body that exhibit a dynamic pH range during normal function or in response to a diseased state [95]

Location	pH
Blood	7.34–7.45
Stomach	1.0–3.0
Upper small intestine	4.8–8.2
Colon	7.0–7.5
Tumor, extracellular	6.5–7.2
Early endosome	6.0–6.5
Late endosome	4.5–5.0
Vagina	3.8–4.5
Inflamed tissue/wound	5.4–7.4

4.2 pH-Responsive Cellulose-Based Hydrogels

4.2.1 Oral Drug Release

Oral administration is the most widely used mode for disease treatment. However, the administration of a medicine at predetermined intervals usually leads to a sawtooth-like rather than a constant drug release profile. Thus, oral drugs with controlled release behavior have gained much attention in recent years.

A sustained-release tablet will pass through the mouth and stomach and finally arrive at the intestinal tracts. The active ingredient in the tablet will be constantly released to the intestine. The normal pH ranges encountered in different organs of the human body are listed in Table 1.

Due to the large difference in the pH between the stomach and intestine, the protection of tablets against corrosion by *succus gastricus* is a critical challenge faced in the field of oral drug release. The expected properties for an ideal hydrogel carrier for oral drug release should include:

1. An appropriate pH-responsive range to ensure that the active ingredients are released at the predetermined location.
2. Desirable biocompatibility and nontoxicity to prevent a rejection reaction by the intestines such as serious gastrointestinal peristalsis.

3. Desirable mucoadhesion to ensure that the tablets can constantly release drugs for a prolonged duration in the intestine without being excreted.
4. Desirable mechanical properties to withstand gastrointestinal peristalsis because the fracture of tablets may result in a sudden release of the drug.
5. Desirable chemical stability so that the tablet can resist corrosion by *succus gastricus*.

Based on the following considerations, pH-responsive hydrogels prepared from CMC exhibit great promise as potential carriers for oral drug release. First, CMC is a water-soluble polymer with desirable biocompatibility. The carboxyl groups in the backbone will result in the shrinkage of the hydrogel's network in the stomach because the pH value of *succus gastricus* is lower than the pK_a of the hydrogel's carboxyl groups. Thus, the drug molecules are protected by the collapsed hydrogel's network rather than being released into the surrounding solution. When the hydrogel enters the intestines, it will absorb water and become swollen because the pH value in the intestines exceeds the pK_a of the carboxyl groups. Thus the preloaded drugs in the hydrogel's network can freely diffuse into the intestines [96]. Second, CMC contains numerous carboxyl groups as well as many residual hydroxyl groups in its backbone, which facilitate the mucoadhesion of this hydrogel onto the intestinal epithelium. Third, anionic CMC backbones can establish electrostatic interactions with cationic polymers, such as chitosan, to enhance the hydrogel's mechanical properties and reduce the risk of a fracture-induced sudden release of the drug [97]. Interestingly, the incorporation of BC provides an effective method for enhancing the hydrogel's mechanical properties because the crystallinity of BC is much higher than that of PC [98]. Fourth, the CMC backbones can be rapidly cross-linked by metal ions, such as Fe^{3+} or Al^{3+}, instead of toxic organic cross-linkers such as glutaraldehyde [99].

Cationic hydrogels can also be used in oral drug release applications. For example, cationic hydrogels can serve as carriers for stomach drugs with poor water solubility, such as curcumin, to ensure they are released over a prolonged duration rather than prematurely excreted from the body [100]. In addition, cellulosic polymers with numerous hydroxyl groups can be quaternized to form cationic hydrogels. The positive charges in the networks can generate weak electrostatic interactions with sialic acid (*N*-acetylneuraminic) in gastric mucus, which can further enhance the residence time of the hydrogel-based drug carrier in the intestines [100, 101].

4.2.2 Vaginal Drug Release

As is the case with oral drug release, pH-responsive cellulose-based hydrogels can also be used in vaginal drug release. It is well known that the pH of semen is ~7.5, while the pH of vaginal fluid is in the range of 3.8–4.5. After sexual behavior, the vaginal fluid will be neutralized to ~7.0. Thus, some anti-HIV agents that have been preloaded in pH-responsive cellulose-based hydrogels can be spontaneously released after sexual behavior due to the variation in the pH value (shown in Fig. 7). In addition, as described in Sect. 4.2.1, due to presence of the ionic groups

on the backbones of cellulosic polymers, the mucoadhesion of these hydrogels will be further enhanced.

4.2.3 Pollutant Absorption

The major pollutants in wastewater that are drained from factories are dyes and heavy metal ions. Both of these pollutants are highly toxic to the human body, and they have been associated with cancers or skin irritation [102]. Generally, absorption is considered to have greater effectiveness for the treatment of dyes and heavy metal ions in comparison with chemical deposition or membrane technologies due to its high efficiency, easy manipulation, and less time consumption [103]. An ideal adsorbent is expected to exhibit the following properties: (1) environment friendliness, (2) affordability, (3) recyclability, and (4) high adsorptive capacity [104].

In comparison with their fossil-based counterparts, biomass-based absorbents have lower preparation costs and better environmental compatibility and biodegradability. As one of the most abundant biomass-based polymers, cellulosic polymers are well-suited for use in the treatment of dyes and heavy metal ions in wastewater. For example, anionic cellulosic hydrogels, such as CMC-based hydrogel, can absorb cationic heavy metal ions or dyes in alkaline media via electrostatic interactions. On the contrary, cationic cellulosic polymers, such as quaternized hydrogel, can absorb anionic heavy metal ions or dyes in acidic media (as shown in Fig. 9). Both of the aforementioned absorption phenomena may be reversible when the external pH is changed [105, 106]. In addition, the abundant -OH groups that are present on the polymer's backbone can be readily modified with other functional groups, which have the ability to selectively bind to particular molecules such as hormones and agricultural chemicals.

4.2.4 Wound Dressings

The faintly acid environment of human skin can inhibit the propagation of bacteria. However, after an injury, the pH of the damaged area will change to an alkalescent value (~7.4) because the tissue fluid and blood exuding from the wound provide ideal conditions for the propagation of bacteria, thus potentially leading to an infection. Therefore, pH-responsive cellulosic hydrogels can serve as wound dressings. For example, quaternized cellulosic hydrogels with excellent hydrophilicity can keep the surface of a wound moist. Meanwhile, cationic quaternary amine groups could inhibit the propagation of bacteria by destroying the bacteria cytomembrane [107]. Anionic cellulosic hydrogels can also be used in wound healing. For example, CMC polymer chains can be readily cross-linked in the presence of metal ions to form 3D networks. Some antibacterial agents such as Ag or ZnO nanoparticles can be entrapped within the networks to endow the hydrogels with excellent antibacterial activity [108, 109]. In addition, other functional molecules such as dextran can be incorporated into hydrogels, thus enabling neovascularization without adding other growth factors [110]. pH-Responsive cellulosic hydrogels can also serve as wound monitors if they are endowed with pH-responsive dyes. Small wounds could thus be detected as soon as possible to prevent infection and facilitate rapid healing (Fig. 10) [111].

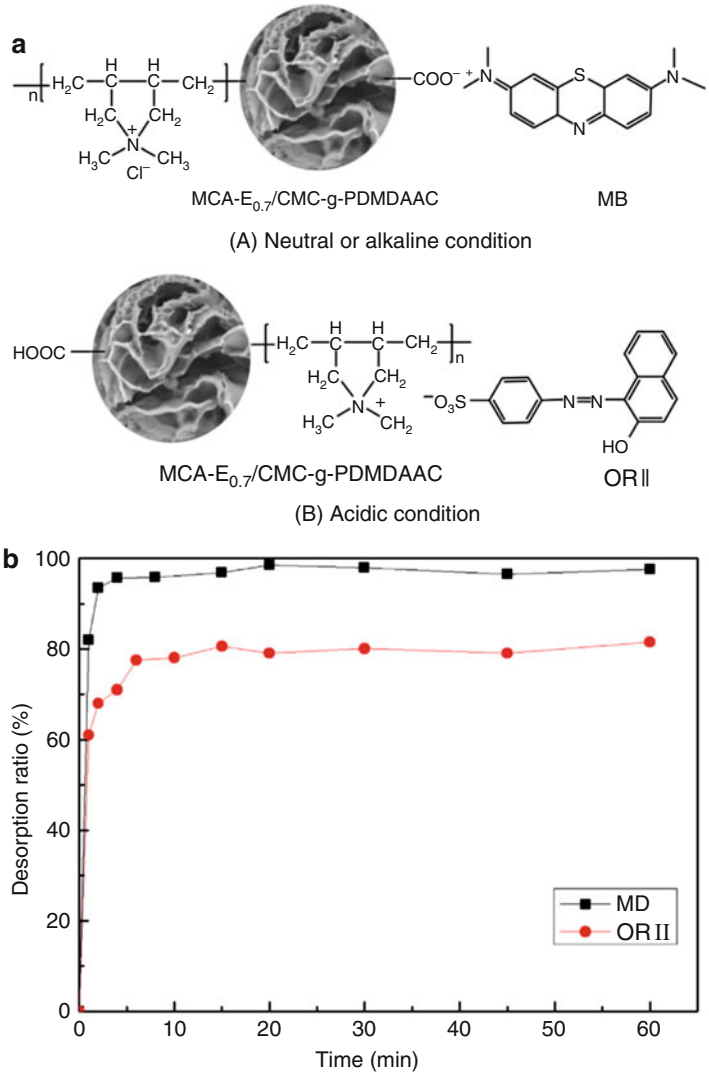

Fig. 9 (**a**) Possible adsorption mechanism of methylene blue (MB, upper) and acid orange II (OR II, lower) on cellulose-based microspheres. (**b**) Desorption ratio of MB and OR II at different times (10 mg of adsorbents; 50 mL of distilled water at pH 3 (MB) or 11 (OR II); room temperature) [105]. (Copyright 2016 Elsevier Ltd.)

4.3 Thermo- and/or pH-Responsive Cellulose-Based Microgels/ Nanogels for Targeted Drug Release

Microgels/nanogels are cross-linked polymeric particles that are each composed of an independent 3D network. As is the case with bulk hydrogels, these micro- or nanoscale hydrogels also exhibit reversible "swell-collapse" behavior to regulate

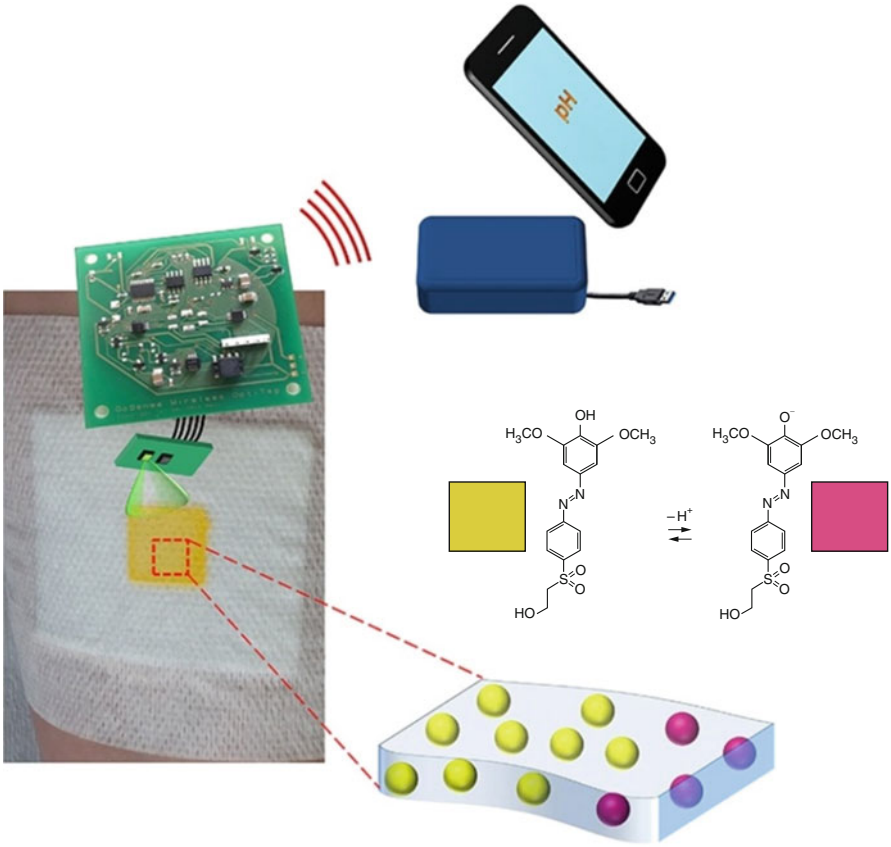

Fig. 10 Schematic diagram illustrating the operation of a wireless smart bandage. The pH-induced color change of cellulose particles that are covalently bound to the hydrogel is measured and sent by a remote unit. Insert is the chemical structures of the protonated and deprotonated forms of hydrogel and their respective color [111]. (Copyright 2017 Elsevier B. V)

their sizes when they are exposed to different stimuli. The diameters of these particles are usually in the nanometer or micrometer range. Microgels/nanogels can serve as conjugates, micelles, or vesicles that mimic microorganisms such as bacteria or viruses, to load molecules such as drugs, proteins, carbohydrates, or DNA/RNA, and transport these molecules into targeted sites within the human body [112]. Thermo- and/or pH-responsive microgels/nanogels are the most widely reported micro-/nanogel drug carriers. In comparison with oral tablets or intravenous injection, they can swell spontaneously, collapse, or disassemble to release drugs to the targeted sites of the human body when they are exposed to external thermal or pH stimuli. This mode of targeted delivery is promising due to the higher drug utilization ratio and the milder drug side effects [113]. In addition to the essential features such as biocompatibility and nontoxicity, the ideal microgel/nanogel carriers are expected to possess the following properties: (1) high drug loading capacities,

(2) desirable chemical stability and mechanical properties to avoid the disassembly or fracture during transport, and (3) sensitive response behavior to ensure rapid drug release in response to the relevant stimuli [114].

Polymeric microgels/nanogels are usually composed of both hydrophilic and hydrophobic polymers. The aforementioned properties are highly dependent on the structures of these hydrophilic and hydrophobic polymers [115]. Based on the following considerations, cellulosic polymers are suitable building blocks for the thermo- and/or pH-responsive microgels/nanogels. First, cellulosic polymers that contain both hydrophilic and hydrophobic groups can serve as surfactants to facilitate the particle formation. The hydrophilic groups such as carboxyl and hydroxyl moieties can improve the water dispersity of gel particles. Meanwhile, the hydrophilic and hydrophobic groups can both form strong intermolecular interactions such as van der Waals forces or associate via exhibiting the hydrophobic effect, to form the cores of the particles [116]. Second, some cellulosic polymers, such as HPMC, MC, HPC, or CMC with remarkable thermo- or pH-responsive behaviors, can be directly employed to create stimuli-responsive gel particles without the need for other fossil-based polymers. Third, some cationic or anionic drugs can form strong noncovalent bonds with the network's backbones via electrostatic interactions without exhibiting undesirable leakage. For example, when the external pH is 7.0, the positively charged anticancer drug doxorubicin (DOX) can associate strongly with the deprotonated backbones of CMC hydrogels. Once the pH is reduced to 6.2 (which is similar to the pH in tumor tissue), the adhesion of DOX will be weakened, which increases the release ratio (Fig. 11) [117]. Fourth, cellulosic polymers bearing numerous hydroxyl groups are excellent candidates for the preparation of amphiphilic graft copolymers with functional side chains, which can spontaneously assemble to form microgels/nanogels [118]. In addition, some reports have demonstrated that graft copolymers exhibited higher drug loading capacities and higher drug releasing ratios in comparison with linear copolymers. The size and structure of nanoparticles prepared from graft copolymers could be easily regulated via changing the structures of the graft copolymers [119–121].

4.4 Photo-Responsive Cellulose-Based Hydrogels

4.4.1 Photo-Reversible Superabsorbents

A superabsorbent is defined as a hydrophilic hydrogel that can absorb and retain extremely large amounts of water relative to its own mass. An ideal superabsorbent should be renewable and exhibit robust mechanical properties. The backbones of the network become fully stretched when the hydrogel is swollen, and the swollen hydrogel may be much more fragile than its collapsed counterpart. Thus, it is of critical importance to enhance the mechanical properties as much as possible to ensure their applicability. The incorporation of highly crystalline cellulose nanofibers is a promising method for improving the mechanical properties of a superabsorbent [122].

Meanwhile, a renewable superabsorbent is highly desirable for practical applications based on cost and environmental considerations. Therefore, a stimuli-

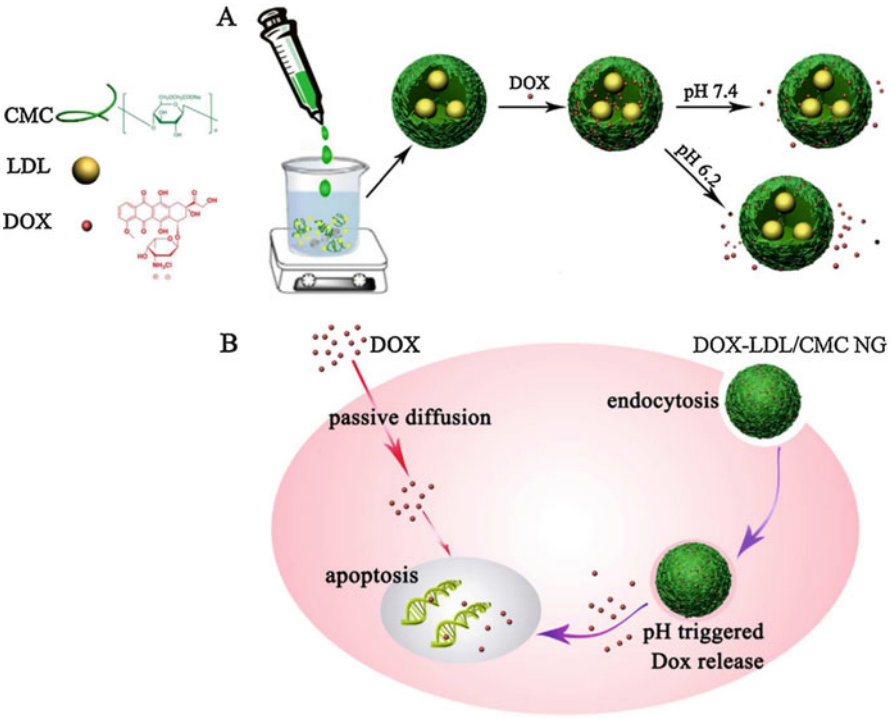

Fig. 11 (**a**) Illustration of the synthesis and structures of LDL/CMC nanogels, DOX loading, and pH-dependent drug release. (**b**) Schematic diagram showing the proposed model for intracellular delivery by DOX-loaded LDL/CMC nanogels to tumor cells [117]. (Copyright 2014 Elsevier B.V)

responsive hydrogel that exhibits reversible "swell-collapse" behavior would be a promising candidate for the preparation of renewable superabsorbents. In comparison to heat and pH, light is an easily manipulated physical stimulus for a renewable superabsorbent because it consumes less energy and chemicals. For example, in situations involving a superabsorbent composed of cellulose nanofibers, a TiO_2 coating exhibiting a photo-triggered "hydrophobic-hydrophilic" transition [123], or possessing a CF3AZO monolayer (Fig. 12) [124], can be deposited or grafted onto the surfaces of cellulose nanofibers. Upon exposure to light, the cellulose nanofibers become hydrophilic, and the superabsorbent thereof can readily absorb water. When the swollen superabsorbent is moved away from light, the cellulose nanofibers will be rendered hydrophobic, and the superabsorbent thereof expels water and thus regenerates itself.

4.4.2 Drug Release Based on Vesicles

Photo-responsive hydrogels can be also used as carriers for photo-triggered drug release thanks to the isomeric reactions of their photo-sensitive components. For example, drug molecules can be loaded into the cavities of vesicles, and the photo-

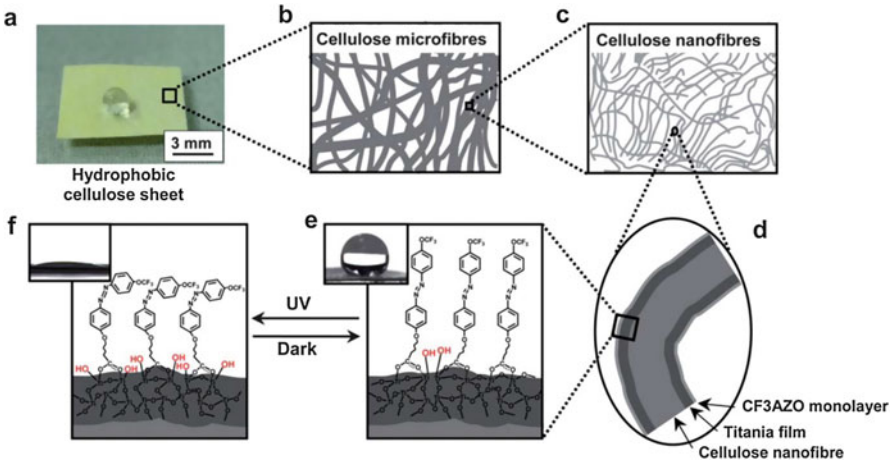

Fig. 12 Schematic illustration of the reversible wettability on the surface of filter paper that is coated by a titania/CF3AZO ultrathin film [124]. (Copyright 2011 The Royal Chemical Society)

responsive hydrogel can serve as the shell layers of these vesicles to prevent the escape of these drug molecules. The hydrogel shell layer can be cross-linked via supramolecular complexation between photo-sensitive guest molecules and cage-like host molecules. Upon exposure to light as a stimulus, photo-sensitive guest molecules can change their conformation and exhibit a lower binding affinity with the host, which provides opportunities for other small molecules to bind with the host molecules. Consequently, the hydrogel shell layer will disassemble, and the drugs within the inner cavity can be released (Fig. 13) [125]. It is also possible to synthesize a variety of derivatives of cellulosic polymers bearing both guest and host molecules via the functionalization of the numerous hydroxyl groups on the polymer backbone [125, 126]. However, light with short wavelengths (such as UV light) is usually unable to penetrate deeply into a material, which limits the applications of photo-responsive hydrogels that can only respond to UV light. Thus, the future studies should be focused on the development of visible or infrared light-responsive hydrogels, as these materials may have greater applicability for in vivo drug release.

4.5 Shear-Responsive Cellulose-Based Injectable Hydrogels

Injectable hydrogels, which are liquid in storage conditions, can be easily injected into target locations via noninvasive implantation. The liquid polymer solution will undergo a "sol-gel" transition via spontaneous physical or chemical cross-linking reactions upon exposure to external stimuli such as heat, pH, particular salt concentration, or shear force. With this in mind, injectable hydrogels are promising candidates for applications in targeted drug release, in cell delivery, or as tissue scaffolds [127].

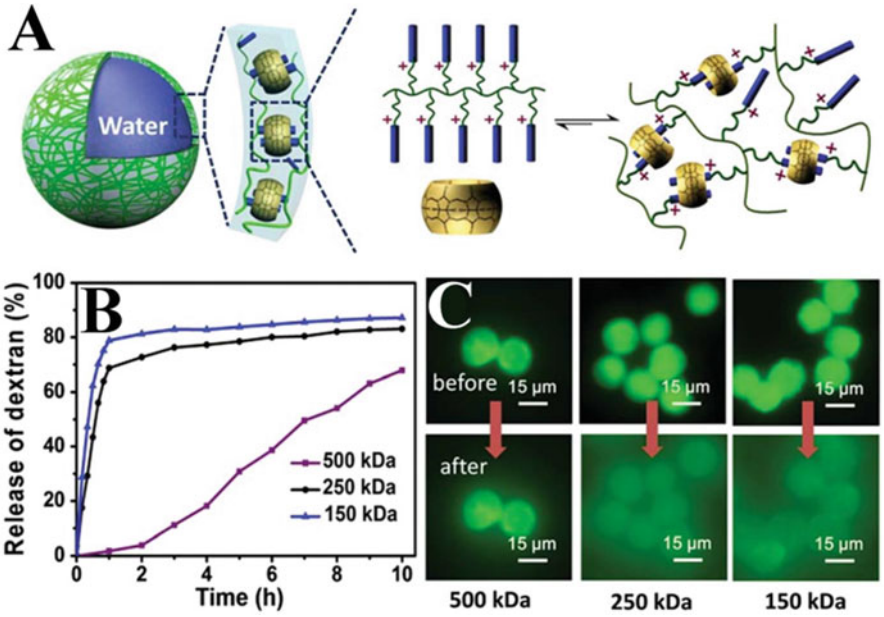

Fig. 13 (**a**) Scheme showing the generation of supramolecular polymer hydrogel shells at a water/oil interface. (**b**) Release profiles of FITC-dextran from microcapsules as a function of the rehydration time. (**c**) Series of fluorescence micrographs of microcapsules loaded with different molecular weight samples of FITC-dextran before and after 2 h of rehydration [125]. (Copyright 2015 The Royal Society of Chemistry)

Shear-responsive hydrogels with shear-thinning behavior are widely used as implantation materials in vivo. Shear-responsive hydrogels are stored in a liquid form. They will be converted to liquid polymer solutions upon the application of an external shearing force. These polymer solutions can be injected into the human body and become gels once again. In comparison to other stimuli-responsive injectable hydrogels, shear-responsive hydrogels have several advantages: (1) The "sol-gel" transition of a shear-responsive hydrogel can occur in an external environment so that the physicochemical properties of the hydrogel can be readily evaluated prior to injection [128]. (2) The gelation behavior of the polymer solution can be precisely controlled because the gelation only depends on the magnitude of the shearing force rather than other complex physical conditions in vivo, such as the pH or the ionic strength [129]. (3) An injected polymer solution can rapidly undergo gelation in the target location instead of spreading to adjacent tissue due to the absence of shearing force [130, 131].

An ideal injectable shear-responsive hydrogel should possess the following properties: (1) All of the components of the hydrogel should be biodegradable and nontoxic, including their by-products after degradation. (2) The required strength of the shearing force triggering the "gel-sol" transition should be within a reasonable range. (3) The viscosity of the hydrogel should decrease rapidly upon the application

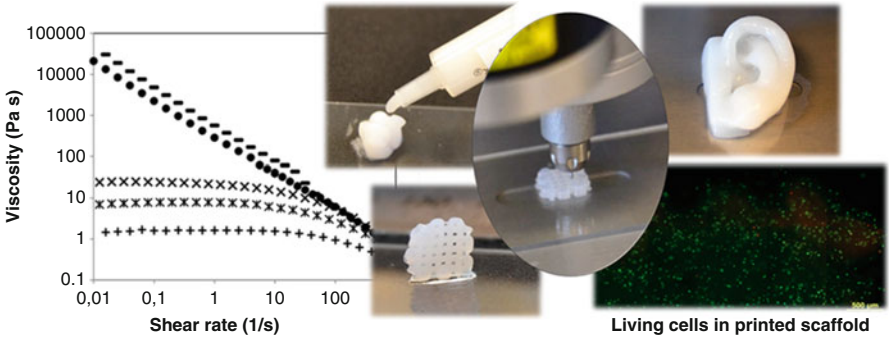

Fig. 14 (Left) Flow curve of a bioink denoted as ink9010 (•), which contains 2.25% nanofibrillated cellulose and 0.25% alginate. (Right) 3D printed small grids and a model of a human ear after cross-linking treatment and the representative images showing dead and live cells in 3D bioprinted constructs after 7 days of incubation in culture media [133]. (Copyright 2015 American Chemical Society)

of a shearing force, and the gelation should also be rapid when the shearing force is withdrawn. (4) The structure and the functions of the hydrogel should be easily regulated. (5) The fabricated hydrogel should exhibit desirable mechanical properties. (6) The hydrogel's biodegradation process should be easily controlled [5].

Shear-responsive hydrogels are promising candidates for applications in drug release, in tissue engineering, and as wound dressings. As discussed earlier, cellulosic polymers have been widely used as building blocks of hydrogels for use in the biomedical fields. For example, cellulosic polymers serve as the backbones that can be modified with cage-like host molecules and guest molecules. The resultant graft copolymers can be spontaneously cross-linked via supramolecular complexation. Drugs can be loaded into the hydrogels and subsequently delivered to a target location when an external shearing force is applied [132]. Furthermore, some biocompatible polymers, such as sodium alginate, can form injectable hydrogels with nanofibrillated cellulose via electrostatic interactions. The resultant injectable hydrogel can serve as a bioink for the fabrication of 3D-printed scaffolds (Fig. 14). The mechanical properties of the resultant scaffolds can be dramatically enhanced through the incorporation of nanofibrillated cellulose [133].

4.6 Electric Field-Responsive Cellulose-Based Hydrogels

4.6.1 Actuators

Electric field-responsive hydrogels can be used as actuators to convert electrical energy into mechanical energy. Muscle fibers are one of the most common examples of actuators, which can become swollen or collapse in response to the application of electric voltage stimuli by neurons. As discussed in Sect. 3.5, electrolyte hydrogels can mimic this behavior via bending or a change in shape upon undergoing morphological transitions in an electric field. They are promising building blocks for the

fabrication of artificial muscles and underwater soft robots [134, 135]. An ideal hydrogel actuator should exhibit the following properties:

1. Excellent mechanical properties to ensure that the actuator can undergo repeatable stretching/shrinking transitions and fine/gross motor movements.
2. Excellent sensitivity to small voltages. In addition, the driving voltage should be below the standard potential at which water undergoes hydrolysis (~1.23 V) to prevent an undesirable electrolysis from occurring and altering the physicochemical properties of the aqueous solution [136].
3. The hydrogel's responsive behavior should be readily adjusted via changing the magnitude of the voltage.

Ensuring that the mechanical properties are suitable is the primary issue regarding the application of an actuator. It has been demonstrated that the incorporation of cellulosic polymers can remarkably enhance the mechanical properties of an actuator. For example, the Young's modulus of an electric field-responsive hydrogel can increase by more than 60% with the incorporation of 1.4 wt% of CMC [136]. On the other hand, cellulosic hydrogels bearing ionic moieties, such as CMC [68] and sulfonated CNC [136], can remarkably enhance the hydrogel's electric responsive behavior due to the presence of ionic moieties in their backbones.

4.6.2 Drug Release

CMC-based electric field-responsive hydrogels can be also used in controlled drug release applications. With the migration of protons within the hydrogel toward the cathode side, the hydrogel will accumulate a negative charge, thus causing the osmotic pressure to increase. Water molecules begin to diffuse into the hydrogel, thus facilitating the release of the drug by the swollen hydrogel with fully stretched networks (Fig. 15) [137]. Although the application of an electrical field to human patients presents a challenge, transdermal drug delivery has been performed via topical electric field techniques such as iontophoresis and electroporation. It has also been demonstrated that electric field-responsive hydrogels can be implanted under the skin and successfully used for pulsed drug release over a prolonged duration [138, 139].

4.7 Magnetic Cellulose-Based Nanogels/Microgels for the Adsorption of Pollutants

The major application of magnetic nanogels/microgels is pollutant treatment. Nanogels/microgels that are loaded with magnetic nanoparticles can migrate along with the direction of a magnetic field and deposit at a particular side of a magnetic field gradient. All of the deposited gel particles can be collected and washed for subsequent use, which reduces the cost of pollutant treatment as well as the risk of residual nanomaterials being released into the natural environment [140]. Usually, the magnetic nanoparticles are incorporated into networks via blending or in situ

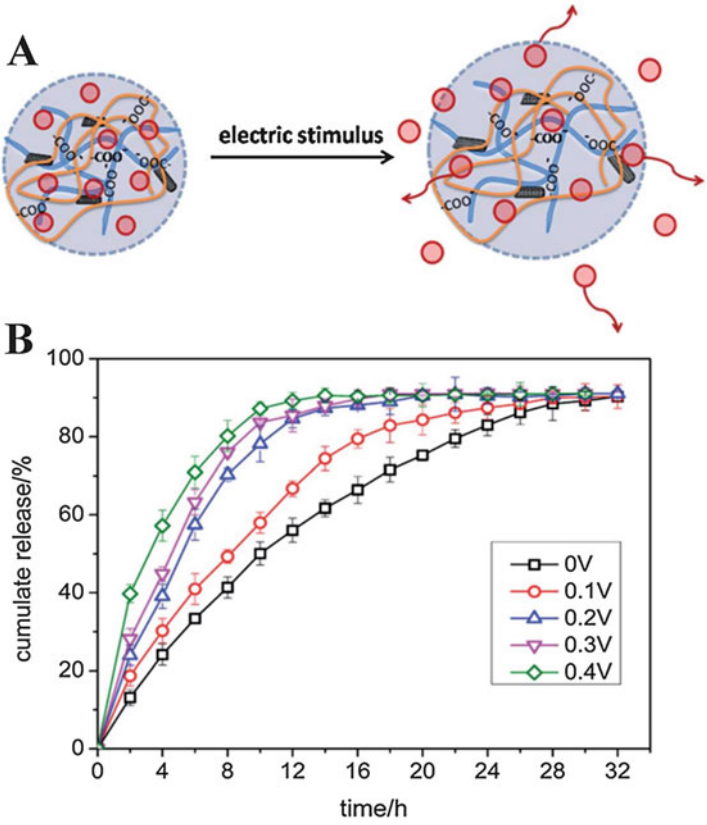

Fig. 15 (**a**) Schematic illustration of electric field-responsive release of ibuprofen molecules from BC/SA/MWCNTs 0.25% hydrogels. (**b**) Amounts of ibuprofen released from BC/SA/MWCNTs 0.25% hydrogels at time *t* at various electric voltages at 37 °C [137]. (Copyright 2015 The Royal Society of Chemistry)

formation. A high loading of magnetic nanoparticles is usually necessary because the rate at which magnetic gels migrate is primarily dependent on the degree of magnetic nanoparticle loading by the gel. However, magnetic nanoparticles may sometimes detach from the gel network and diffuse into water during usage, which will inhibit the magnetic migration. Thus, the two critical parameters for the application of nanogels/microgels are (1) the stability of the magnetic nanoparticles during the usage as well as (2) the loading degree of the magnetic nanoparticles in the gel network [72].

Based on the following three considerations, cellulosic polymers are suitable precursors for matrices of magnetic nanogels/microgels. First, a cellulosic polymer matrix facilitates the immobilization of magnetic nanoparticles, and the detachment of these nanoparticles can be prevented because the cellulose backbones contain many polar groups that interact strongly with the magnetic nanoparticles [141].

Second, any residual nanogels/microgels that are released into the environment can be decomposed by microorganisms in the natural world due to the biodegradability of the cellulosic polymer matrix, which helps minimize the environmental footprint of these materials. Third, cellulosic polymers are abundant and cheap, which facilitates the large-scale fabrication and application of magnetic nanogels/microgels. In addition, the carboxyl groups of CMC can serve as the active sites for the in situ formation of magnetic nanoparticles. The numerous active hydroxyl groups in cellulose can potentially be modified into other functional groups, such as vinyl groups, to form robust covalent bonds with magnetic nanoparticles, thus preventing their detachment.

Another promising application of magnetic cellulose-based nanogels/microgels is their 3D assembly in tissue engineering. For example, nanogels/microgels could be assembled in predesigned arrangements orders, and their stacking sequence could be easily controlled via regulating the direction of a magnetic field. This may be a promising strategy for the preparation of highly ordered hydrogel materials with well-defined structures and advanced functionality [142].

5 Conclusion

Stimuli-responsive hydrogels have been widely used in numerous fields, such as targeted drug delivery and controlled release, mass separation, soft machines, sensors and/or actuators, scaffolds for tissue engineering applications, and so on. The incorporation of cellulose into stimuli-responsive hydrogels helps to enhance the mechanical properties of the hydrogels, improving their biocompatibility, biodegradability, and mucoadhesion and also provides a facile means to synthesize gels. Cellulose-based stimuli-responsive hydrogels can serve as the key components of membranes, bulk hydrogels, microgels/nanogels, and injectable hydrogels. The properties of hydrogel-based materials that are used in these fields are significantly improved via the use of cellulose as a component. Cellulose-based stimuli-responsive hydrogels have excellent potential for use in drug delivery/control release, wound dressings, scaffolds for tissue engineering, absorbent materials, and actuators.

6 Future Outlook

Cellulose-based stimuli-responsive hydrogels combine the features between cellulose chemistry and stimuli-responsive materials. Therefore, the development of cellulose-based stimuli-responsive hydrogels is highly dependent on advances made in these two fields. Some of the following challenges may need to be addressed and investigated further in order to facilitate potential applications of cellulose-based stimuli-responsive hydrogels in the future.

1. The regioselective reactions for preparing cellulose derivatives are still limited, and more investigations remain necessary. The exhilarating results in this field facilitate the combination of cellulosic polymers with other novel stimuli-responsive groups or polymers. Some novel cellulose derivatives may exhibit improved biocompatibility, mucoadhesion, or distinctive responsive behaviors when compared to conventional cellulose derivatives.
2. Nanofabricated cellulose and cellulose nanocrystals can greatly enhance the mechanical properties of hydrogels. Their surface modification technologies and their morphology regulation will demand much attention because addressing these challenges may enable researchers to greatly enhance the mechanical properties of hydrogels. In addition, the dispersity of crystalline cellulose in water as well as its miscibility with other functional polymers warrants attention.
3. In comparison to other polysaccharides, i.e., chitosan and dextran, the biodegradability of cellulosic polymers, especially for nanofabricated cellulose and cellulose nanocrystals, still requires improvement. Notable examples include achieving control over their degradation rate and behavior in physiological environments.
4. The most prominent merit of cellulose-based materials is their low cost. An amount of cellulose-based stimuli-responsive hydrogels with novel functions and complicated structures have been successfully prepared and applied in the laboratory. However, their preparation cost is still an area of concern and is an important factor for their large-scale fabrication and application in the future.
5. Thermo- and pH-responsive hydrogels are currently the most widely studied classes of stimuli-responsive hydrogels, and the further studies should be devoted toward the development of hydrogels with narrow and accurately defined response ranges. Furthermore, their response regions should be easily regulated to facilitate their use in many fields.
6. Light is an easily manipulated physical stimulus compared to heat and pH. However, the application of UV light-responsive hydrogels in vivo is usually limited. Future research should be focused on the development of hydrogels that can respond to visible and infrared light.
7. Compared to heat and pH stimuli, non-contacting stimuli, such as light, electrical fields, and magnetic fields, have greater potential because they can be easily controlled and adjusted in terms of time and space. However, these stimuli have received relatively little attention.

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Enzyme-Responsive Hydrogels

10

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Abstract

In an enzymatically responsive system, a suitable enzyme is used as a stimulus for a control release or delivery at a specifically targeted site where that enzyme is designed in such a way that can work at certain controlled conditions (such as temperature, pH). Enzyme-responsive hydrogels prepared from cellulose along with other materials have suitable macromolecular networks and can work in controlled environment. Specifically designed enzymatic stimuli-responsive system, one of the highly explored techniques, popularly explored to add a triggerable agent (such as a polymer or a lipid) that can encapsulate the active component in a protective manner. Usually, this active agent is responsive to degradation or swelling when it reaches at the target site. An enzymatic stimulus-responsive system is highly attractive field of research due to its many potential applications (e.g., in controlled release, drug delivery, and other areas of life and material sciences). This chapter gives a brief overview on the design and uses of enzyme-responsive hydrogels based on cellulose and other polymers for their various applications in different fields including in controlled drug delivery and other areas of biomedical and material sciences.

Keywords

Cellulose · Hydrogels · Enzyme · Enzyme-responsive hydrogels · Stimuli-responsive hydrogels · Drug delivery · Biomedical

1 Introduction

Hydrogels are substances that absorb significant quantities of water, and usually they are prepared from natural materials. They are widely studied all around the world for their enormous biomedical applications [1–4]. The attractive characters of hydrogels stimulate scientists for continuous investigation on novel biomaterials for their potential industrial applications. Hydrogels have the capability to absorb large quantities of water due to their three-dimensional polymer networks, and this morphological structure also modifies their characters to allow them to be soft and pliable as well as to retain structural water which makes them suitable for many conventional and potential biomedical uses. Recently, hydrogels are popular for a variety of biomedical

applications [5–12]. Because of the high water content of hydrogels, they are compatible to most of the living tissues, and their viscoelastic nature also contributes to reduce the damage to the surrounding tissue when implanted in the host system [13–15]. Besides this, the mechanical characters of hydrogels are parallel to those of soft tissues which are particularly attractive for tissue engineering applications. Bioactive materials are frequently used for hydrogel synthesis, and these materials can interact with the host tissues to assist and improve the healing process as well as to mimic functional and morphological properties of organ tissues [13–18]. Hydrogels can also be made by using biomaterials along with smart materials in order to offer natural adaptations (e.g., sensing devices, controlled actuations, regulation of target functions, control in feedback systems). This type of stimuli-responsive hydrogels is capable to adapt with the required changes in their surrounding environmental stimuli (for instance, surrounding composition, presence of enzyme, temperature, pH, light) [19–28]. Smart hydrogels are attractive for their practical and potential uses as biomimetic materials and for their applications in biosensors, processors, and also in activators for electrical responses [29–33]. As for example, the frequent uses of electroconductive hydrogels (such as in bio-recognition membranes for implantation of biosensors, fabrication of drug-eluting devices based on electrically stimulated hydrogels, and also in low interfacial impedance layers of neuronal prostheses based on hydrogels) have been successful to open new horizons in the fabrication of devices for biomedical detection purposes. One of the main reasons for this success is based on the fact that both biomolecular recognitions and responsive functions based on biomolecular targets and induced structural changes can be incorporated into the structural networks of hydrogels using meticulous preparation techniques and skillful design strategies [34–36]. In order for an effective therapeutic delivery, monitoring, and molecular imaging (using noninvasive techniques) to detect and treat different diseases, hydrogel-based drug delivery systems are popularly used since hydrogels provide the required feasibilities for the integration of smart systems and biomolecular imaging. As a result, this type of smart hydrogels can be used for self-regulation and controlling hydrogel-based devices for maintaining physiological variables (suitable for drug delivery and cell culture applications) [37, 38]. For drug delivery, hydrogel implantation can be carried out by preforming or injecting; however, the preformed hydrogels are usually processed by using active reagent in vitro before in vivo implantation. In biological sciences hydrogels are widely used in different areas, because both the intracellular cytoskeleton and extracellular matrix (ECM) are compatible with gel-phase materials. For example, biological gels can be designed to show responsive characters when they are exposed to suitable changes in their environment using different methods including specific enzymatic processes that involve adaption and reorganization of gel structures [39–47]. Both adaption and reorganization are very important to different processes within cell cultures (e.g., differentiation and cell division). Thus, the production of synthetic mimics of hydrogels is critically important as they can be used to measure and direct different biological processes. Enzyme-responsive hydrogels can be applied to mimic biological matrices, and different enzymatic processes have the feasibility to fabricate enzyme-assisted assembly of gels with precisely controlled characters [48–50].

Hydrogels have been widely used for various applications for a long time. For example, since the 1960s, synthetic hydrogels have been applied in biomedical uses,

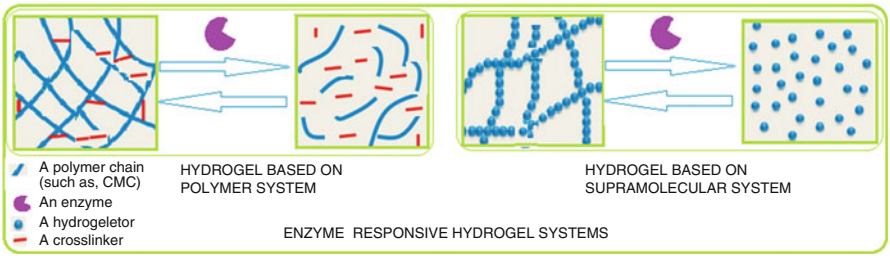

Fig. 1 A schematic representation of an enzymatic stimulus-responsive system

which at that time Wichterle and Lim illustrated the use of biocompatible hydrogels prepared by cross-linking poly(hydroxyethylmethacrylic)acid [poly(HEMA)] in contact lenses [49]. In 1980 naturally derived hydrogels (such as based on alginates) were reported and used to encapsulate pancreatic cells [50], which was then followed by the application of shark collagen in the dressings of burn wounds [51]. Both synthetic and natural materials are frequently used in hydrogel formations; however, currently hybrid systems are being rigorously investigated for their vivid benefits [52]. In previous studies on hydrogels, mostly structural properties of hydrogels that can effectively match natural tissues were used to be studied most rigorously; however, this focus has been shifted to the synthesis of materials that can match structurally and chemically as well as have the capability to mimic aspects of biological gels. As for instance, hydrogels are being designed in such a way which can retain short peptides, sugars, or other biomolecules in order to facilitate suitable interactions with biological systems. Recent progress in this field is mostly focused on the control degradation using enzymatic action to design biomaterials [48]. The application of enzymes in the fabrication of materials is significantly important because of their selectivity and synthetic capability under mild conditions [48]. Synthetics gels can be divided into two groups considering the chemical nature of their networks; they are (a) polymeric hydrogels and (b) supramolecular hydrogels (Fig. 1). Typically, polymeric hydrogels are covalently cross-linked networks that illustrate swelling characters because of the absorption and ability to trap water in their structures [49]. However, supramolecular hydrogels generally show reversible, non-covalent molecular interactions (such as hydrogen bonding, pi stacking, electrostatic and hydrophobic interactions, van der Waals forces) between self-assembling molecules (also termed as hydrogelators) to form nanofibers. Depending on their surface chemistry, these nanofibers are entangled into 3D networks that provide the capability to trap water and form hydrogels [52, 53]. This chapter briefly presents selective aspects of enzyme-responsive hydrogels and their applications in specific areas.

2 Enzymatic Stimuli-Responsive Hydrogels

Environmental stimuli-responsive materials have the capability to change form and/or function when exposed to environmental stimuli (or cues); some of the widely used environmental stimuli include pH, temperature, light, and electric fields

[49–51]. Suitable portable electronic devices based on stimuli-responsive materials have variety of applications in different branches of science and technology as well as in every-day life. These materials are highly sought for many advanced applications in a variety of areas (e.g., in electronics [52], healthcare [53, 54], and energy creation and storage) [55]. The stimulus or trigger used for induction on the stimuli-responsive materials causes a change or a combination of different changes on the characters of the exposed material which is a very important part of the responsive material technology suitable to design many controlled features of certain material properties. Enzymes have some sort of decisive control on different processes of living organisms, and thus enzymatic stimuli-responsive materials can be used to design a wide range of materials including artificial biological materials to perform desired activities [56, 57]. Enzyme-responsive materials (ERMs) change their functionality when they are exposed to the action of a particular enzyme or a combination of enzymes. Enzyme-responsive hydrogels are usually designed and synthesized for enzyme-responsive materials [4, 58–62]. The practical use of enzyme-responsive materials is a gradually increasing phenomenon in light of the inspiration for biologically compatible synthetic technologies to mimic natural environments. For example, in biological systems enzymes take part in a plethora of biochemical reactions which have effective influences on different nanoscale processes which include (a) protein expression, (b) formation of cellular adhesions, (c) signal transduction, and (d) macroscale processes such as (a) cell movement and (b) muscle contraction [57, 63]. In enzyme-responsive materials, enzymes control the specificity, selectivity, and the catalytic efficiency of the host materials [63–65]. Figure 1 shows a schematic presentation of enzyme-responsive materials based on polymeric (in the left side) and supramolecular hydrogels (in the right side). Enzymatic processes may be exploited in both the degradation and the controlled assembly of hydrogel materials. Recent investigations illustrated that the stem cell growth and differentiation (in addition to biochemical signals) are strongly influenced and show sensitivity toward suitable physical stimuli that exist within the range of their surrounding environment [56].

Enzyme as a stimulus is very often used to perform a certain piece of work in order to control material properties. A wide range of enzyme-responsive materials are used to carry out different ranges of selective activities. For example, different enzymes are used in enzyme-responsive materials where some of the most frequently used enzyme classes include (a) proteases, (b) kinases, (c) phosphatases, and (d) endonucleases. Proteases and endonucleases are capable to cleave peptides and oligonucleotides, respectively; they have their usual applications in the degradation or disassembly of enzyme-responsive materials. In addition, they are also capable to cleave functional groups from enzyme-responsive materials which make the materials suitable for a variety of sensing applications. On the contrary, enzymes with covalent bond formation capability (e.g., transglutaminases) can be applied for enhancing the structural strength of enzyme-responsive materials by allowing the formation of cross-links within the material [48, 56–59]. Generally, sophisticated methods are used to apply the hydrolytic properties of proteases and endonucleases as enzymatic triggers for initiating overall changes on the properties of the enzyme-

responsive materials. Additionally, phosphatases and kinases are also frequently used because of their complementary catalytic actions. For example, kinases are popular enzymes for phosphorylation of molecules during the presence of adenosine-5′-triphosphate and phosphatases are used for dephosphorylation reaction. Antagonistic interplay of this type of enzymes provides the scope of designing reversible enzyme-responsive materials with dynamic properties. The level of enzymatic interaction between enzymes and different enzyme-responsive materials is sometimes distinctly different from enzymatic reactions which involve solubilized substrates. As for instance, the usual use of kinetic models for stating the enzymatic conversion of solubilized substrates (such as Michaelis-Menten kinetics) cannot be employed for enzyme-responsive materials when the materials are significantly large in size (and show relatively lower mobility compared to that of the enzyme). Most enzyme-responsive materials (such as hydrogels, surfaces, particles) where the enzymes are expected to move toward the substrates show similar behavior. Moreover, it is also possible that aspects relating to diffusion kinetics where substrates bound to other materials may also exhibit a difference in characters than from the properties of solubilized substrates with respect to enzyme specificity and steric effects. As a result, for designing efficient enzyme-responsive materials, different important factors are usually considered, some of which are (a) the chemical and physical characters of the material, (b) the concentration of the enzyme present in substrate/material, and (c) the method in which the substrate is anchored to the material [64–66]. In addition, a longtime goal of the research activities on hydrogel is focused on the way to develop stimuli-responsive hydrogels with potential controls on external features relating to cell encapsulation or release of actives. Stimuli-responsive smart or intelligent hydrogels are those gels which may display property or functionality changes in response to variations in the external environment. Typically, these changes in their surroundings involve solvent polarity, temperature, pH, supply of electric field, light, etc. [4, 59]. More generally, materials based on stimuli-responsive technologies are increasingly attracting attention due to their potential applications in everyday life, offering improvements in many technologies [48, 60, 61]. There are excellent reviews on this topic that discusses the design, advantages, and challenges of stimuli-responsive hydrogels [56, 62]. In cellular environments, most stimuli-responsive mechanisms take place under the control of enzymes [63]. Compared with physical or conventional chemical stimuli (e.g., pH, temperature, ionic strength, ligand-receptor interactions), enzymatic regulation of material properties shows much promise because it enables responsiveness to biological signals, which are highly selective and involve catalytic amplification to enable fast response times [64]. Both polymeric and supramolecular hydrogels are useful [65] which can be used to degrade matrices in a controlled fashion using suitable methods, such as by incorporating enzyme-responsive materials into the structural compositions of the hydrogels. So, by doing this it is possible to design hydrogels with the capability of controlling degradation by using different ways including the breaking of chemical cross-links (polymeric hydrogels) or controlled disassembly (supramolecular hydrogels) (Fig. 1). As it is possible to carry out enzymatic degradation selectively and precisely using suitable techniques and

materials, enzyme-responsive hydrogels are highly attractive field of current active research for their huge application potentials in different areas of science and technology [66, 67].

2.1 Biocatalytic Assembly of Supramolecular Polymer-Based Enzyme-Responsive Hydrogels

In general, dynamic processes in biological systems can be controlled by two spatially confined molecular mechanisms; they are (a) catalysis and (b) molecular recognition. The working principles are a bit different for the biological system compared to that of other traditional methods usually used to control supramolecular synthesis that typically uses the change in one or more of the environmental conditions (e.g., pH [68], temperature [69], solvent polarity [66], and/or ionic strength [67]). For over the last two decades or so, enzymes have been popularly used for direct supramolecular assembly [48, 70, 71] due to a number of reasons including the relative ease in biocatalysis. Some advantages of biocatalysis performed in this way are (a) easy responsive assembly under constant, physiological conditions [72], (b) exploitation of biocatalytic reactions particularly relating to certain cell types or diseased states [64, 73], (c) easy inherent catalysis involving molecular amplification (turnover numbers approx. 10^3–10^7) that facilitates fast response time, (d) new tools for bottom-up nanofabrication by taking advantage of the ability to spatially and kinetically control the self-assembly process [72–74], and (e) thermodynamical control systems with routes toward the discovery of peptide-based nanostructures by using reversible exchange of amino acid sequences in dynamic peptide libraries. Additionally, biocatalytic self-assembly forms gelators by using enzymatic reactions (either through hydrolysis or condensation of precursors) followed by the self-assembly of these molecules to form supramolecular structures. These assemblies, in turn, entangle to form different nanostructures (such as 1D, 2D, or 3D nanostructures) (Fig. 2) through different non-covalent interactions that include (a) π-π interactions, (b) hydrogen bonding, and (c) electrostatic interactions [75–79].

2.2 Designing Enzyme-Responsive Materials

Generally, a wide range of issues are properly considered for the design of high-quality enzyme-responsive materials very selectively, and two of them are briefly included here.

2.2.1 Operational Capability

Enzyme-responsive materials are expected to maintain enzymatic activity under specific operational conditions or given environmental conditions (such as aqueous environments at neutral, basic, acidic pH, other selected ionic conditions). Particular types of synthetic materials (e.g., polymers or inorganic particles) sometimes can

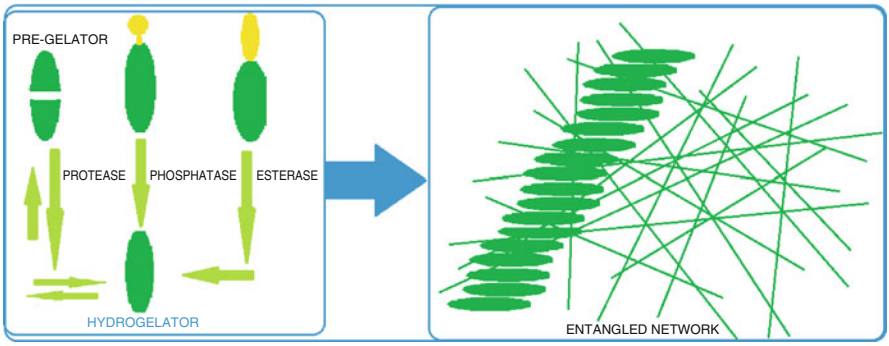

Fig. 2 Schematic illustration of enzyme-assisted self-assembly. The enzyme action results in the formation of hydrogelators which are able to self-assemble to form supramolecular structures and then entangle to form a network

work under this type of environmental condition. As for instance, poly(ethylene glycol) [66], dextran [67, 70], amylose [80], gold [81, 82], and silica [71, 72] nanoparticles and selected peptide-based materials [73, 74] are successfully used to design environmental stimuli-responsive materials.

2.2.2 Meeting Specific Design Requirements

Environmental stimuli-responsive materials are expected to carry out enzymatic activity and other stipulated functions by fulfilling certain design requirements. Some of these requirements include (a) the presence of an active enzyme-sensitive part, (b) translation of enzymatic action of the enzyme-sensitive part to the rest of the material, and (c) sufficient contribution for an effective change in the overall character of the material.

2.3 Specific Characteristics of Enzyme-Responsive Materials for Market Applications

2.3.1 Typical Natures of Enzymatically Responsive Systems

Enzymes have one of the unique control mechanisms usually observed within natural substances in order to regulate the complex biological processes which are by far not matched by the artificially developed systems. As a result one of the main objectives to design enzyme-responsive materials is to synthesize suitable materials with capabilities to replace or at least a comprehensive interaction with natural biological systems. The strength of enzymatically controlled material characteristic depends on the feasibility to design the required material response which is totally influenced and controlled by the biological systems present in the surrounding environment for an ultimate goal to assimilate the environmentally responsive materials into a biological process. However, due to biological complexity, there are tough challenges to develop enzyme-responsive materials with tremendous

application potential to carry out particular jobs on cue when prompted by an enzyme. Enzyme-responsive systems have been widely used in different areas of science and technology including (a) enzyme diagnostic systems [56, 86], (b) drug delivery systems [9, 74, 83–88], and (c) different areas of regenerative medicine [74]. For example, in order to detect different enzymes and their enzymatic activities, different types of enzyme-responsive particles have been developed. Additionally, because of aggregation or dispersion of particles and also due to a particular type of control, the quenching activity of quantum dots, usually the detection of enzyme, depends on the change in magnetic or spectroscopic characters [56, 89] where some of these systems are sensitive even in low level of enzyme concentration [9]. Enzymatic stimuli-responsive hydrogels are frequently used for targeted drug delivery, while the strength of enzymatically controlled drug delivery depends on the ability to allow drug release when it is required in the presence of specific enzymes. Higher levels of specific enzymes are related to different diseases; hence suitable markers and stimuli for the spatially and temporally targeted delivery of therapeutics are important. Thus, for a simultaneous treatment of the diseased tissue and the measurement of the effect of the treatment, the impact of environmentally responsive hydrogels, especially enzymatic stimuli-responsive hydrogels, has many special significance. As for instance, regenerative medicine constitutes a wide range of biomedical research where enzymatic stimuli-responsive materials are frequently used along with the association of many functional polymers or nanomaterials or biomaterials. Some specific applications out of many other important uses of enzymatic stimuli-responsive materials and enzymatic stimuli-responsive hydrogels include (a) applications of enzymatic stimuli-responsive materials or enzymatic stimuli-responsive hydrogels in the formation and degradation of hydrogels as artificial cell supports [74], (b) the enzymatic control of surface properties to control cell response [9, 85], and (c) the enzyme-triggered release of bioactive molecules (such as growth factors) [48, 53–55, 58, 59].

2.3.2 Matching Enzymes and Materials to Specific Applications

Selection of right enzymes or ESM exerts challenges during the design of environmentally responsive materials; however, different model enzymes are sometimes conveniently used to illustrate the mechanism of an ERM. This type of system is useful when the material used can show good performance under the specific conditions present in its surrounding environment. The target enzymes should have the ability to affect only the ESF in the material in order to leave the rest of the material unchanged for minimizing the chances of non-specific responses. Additionally, different strategies which have been developed for realizing the same material response should be reflective of the need to have a versatile repertoire of ERMs that can be adapted for a particular application. Undesirable effects of the biological environment on the material should be avoided, apart from some responsiveness characters, such as response to the marker enzyme and inertness of the environmentally responsive materials to other components present in the system (such as other enzymes, pH, and temperature). In this context, many ERMs have been synthesized and developed that have the capability to respond to an enzyme

with a high specificity to a particular substrate [26, 90]. On the contrary, when enzyme-responsive materials are unable to display the required specificity to a particular enzyme, they have limited application potential. For enzyme-responsive materials where longer peptide or DNA sequences are used that may be recognized by other enzymes and to ensure high impact applications of ERMs, these types of issues need to be resolved. For example, several ERMs with simple ESF (di- or tripeptides that are only sensitive to very specific enzymes) or intentionally broad enzyme specificity have been reported to perform well in in vitro studies that include the formation of supramolecular hydrogels inside cells and polymer hydrogel degradation [26–28, 66, 87, 91].

2.3.3 Choosing the Enzyme Response Mechanism

In case when a particular type of mechanism employed to translate enzymatic action into a material, response has to be tailored to the enzyme catalytic action if a target enzyme has been selected for a specific application. Since both bond formation and cleavage have been employed to date, the bond cleavage has been the more popular choice for existing ERMs. Besides this, some new methods have been applied in order to have opposite material responses with the similar type of enzymatic reaction, for example, enzymatic cleavage of peptide sequences on metal nanoparticles has been used to cause both aggregation and dispersion of the particles [28, 30]. In addition, current trends to enhance different targeted properties of enzyme-responsive materials are more focused on relatively higher dynamic or reversible systems that illustrate a shift from a single-time use of enzyme-responsive materials. Moreover, the introduction of functional characters with a capability to be controlled reversibly and/or on an on-demand basis is another level of progress for a relatively more precise type of incorporation of ERMs into a biological system. Different targeted applications where phosphatases and kinases play significantly important roles are useful for this due to their natural design to catalyze opposite reactions. Reversible enzyme-responsive materials are usually based on a phosphatase/kinase system, although nucleases and ligases perform similar functions (cleavage and bond formation between nucleotides); one example of an enzyme-responsive material is well known where the DNA strands are chemically reconnected after enzymatic cleavage [26–28, 40].

2.3.4 A Brief Discussion on the Enzyme Kinetics of Enzyme-Responsive Hydrogels

A full understanding on enzyme-substrate interactions and the manipulations of these interactions relating to enzymatic control on the suitable drug delivery systems based on enzyme-responsive hydrogels requires a basic understanding on certain aspects of enzyme kinetics, which is briefly outlined here in Fig. 3. The enzyme and substrate must interact to bind together for a conversion of a substrate (S) into a desired product (P), and in that stage the substrate gradually starts to convert into to the product by the enzymatic reaction depending on a range of influencing factors (such as temperature and pH of the surrounding environment, nature of the substrates and enzymes used, amount of both substrates and enzymes used, time of enzymatic

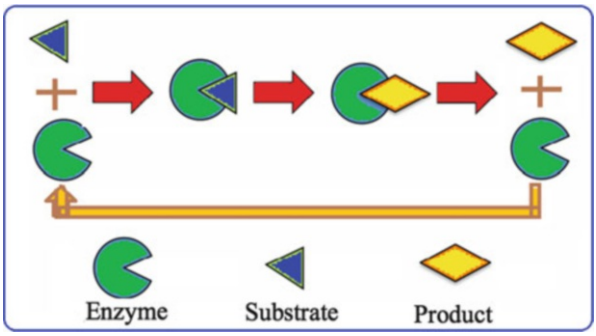

Fig. 3 A schematic representation of enzyme-substrate interactions and the manipulations of these interactions relating to enzymatic control on the suitable drug delivery systems based on enzyme-responsive hydrogels

reaction, etc.). At the final stage, the product is released by the action of enzyme (as demonstrated in Fig. 3). Figure 3 also demonstrates the mechanism by which enzyme specificity occurs using the "lock and key" mechanism. In this case, each enzyme has an active site (termed as lock) to which substrates of proper conformation (termed as key) must bind together and interact to cause a change in chemical structure. However, this change in chemical structure contributes to regulate the specificity of the enzymes in such a way to ensure that only specific substrates with the proper conformations have the capability to bind to the lock and undergo enzymatic conversion into product [27, 28, 92]. For instance, Fig. 3 exhibits a circular substrate would not be converted to product as it would not properly fit in the triangular lock.

2.4 Selective Examples of the Synthesis of Enzyme-Degradable Self-Assembled Hydrogels

Nowadays hydrogels are rigorously studied due to their different applications in various areas of science and technology; some applications include well-defined controlled release of bioactive molecules (such as proteins) and encapsulation of living cells. Biodegradability of hydrogels is one of the very interesting features of controlled drug delivery systems where the original three-dimensional structure has the capability to be disintegrated into nontoxic substances to ensure biocompatibility of the gel. Chemical cross-linking is a frequently used popular method to synthesize mechanically robust hydrogels, but the cross-linkers used in hydrogel preparation require to be extracted from the hydrogels before any suitable application because of toxic nature of the used cross-linkers. In this context, physically cross-linking techniques are preferred alternatives for preparation of hydrogels. Additionally, enzymes are also used for cross-linking to perform specific operations where most of the enzymes are usually used for biodegradation. The generation of a range of star-shaped block copolymers composed of a biocompatible poly(ethylene glycol) (PEG) core tethered to a polyalanine (PAla) shell that possesses the capability to (reversibly) self-assemble in water is a very interesting and important way of producing biodegradable hydrogels. The hydrogels formed in this way offer a

hydrophilic environment that is compatible to different biological processes involving proteins and are able to withhold albumin for prolonged periods before its triggered release following the targeted material degradation by a proteolytic enzyme (such as elastase). Thus, the hydrogels prepared in this way provide a promising opportunity to deliver proteins (and inhibitors, to some extent) in response to a proteolytic enzyme overexpressed in chronic wounds [27, 28, 46–48, 88, 92].

3 Applications of Enzyme-Responsive Systems

3.1 Biomedical Applications of Enzyme-Responsive Hydrogels

Enzyme-responsive hydrogels especially based on peptide self-assembly are attractive biomaterials because of their huge application potentials where some of the principal uses include (a) cell culture, (b) drug delivery, (c) biosensing, and (d) proving the scope for a dynamic control and regulation of cell fate by using systems with intracellular operation capability. So, in brief, the potential biomedical applications of enzyme-responsive hydrogels include (a) control and direction of cell fate, (b) imaging and biosensing, (c) controlled drug release, and (d) applications in cell scaffolds and tissue engineering [93–107]. Regenerative medicine, is a fast-growing area of science and technology. Different researcher groups are constantly working in different issues where devising and upgrading useful techniques and methods for repairing diseased or injured tissues are continuously investigated. Currently, stem cells are being rigorously studied because of their different aspects relating to embryogenesis, homeostatic turnover, and normal tissue repair. In order to realize the potential, stem cell-based therapies are still required to meet criteria in a clinical setting because of different issues including (a) number limitation, (b) immunogenicity, (c) tumor formation, and (d) ethical considerations surrounding their usages. Additionally, the stem cell differentiation mechanisms are complicated and very difficult to understand; hence expanding stem cell numbers and predictably directing their commitment to a desired lineage is very challenging (particularly, to devise tissue regeneration strategies). Different research groups are engaged with continuous research activities to realize the full potentials of enzyme-responsive hydrogels for tissue engineering applications particularly in the area of regenerative medicines [93–107].

3.2 Application of Enzyme-Responsive Hydrogels in Drug Delivery and Bioelectronics

Usually, enzyme-responsive materials have an enzyme-sensitive part along with another part that can direct or control the level of interactions in order to lead macroscopic transitions. Enzyme-responsive materials have many advantages over pH- and temperature-responsive materials, and all these types of materials can be used for stimuli-responsive hydrogels using suitable chemistry and methods. When

an enzyme-responsive hydrogel is applied on a target substrate, the catalytic action of the enzyme on the substrate can lead to different changes that include (a) changes in supramolecular architectures and (b) swelling/collapse behavior or the surface transformation of the substrate. In addition, the sensitivity of the enzyme as a stimulus is unique as enzymes are highly selective in their reactivity and they have the capability to operate under mild conditions present in vivo (a vital case for many biological pathways). The stimulus does not need to be added externally but can be supplied by the biological environment itself as many enzymes are already present in the body. When the naturally present enzyme matches with the triggering enzyme of the responsive material-based hydrogel system, it is more effective for particular type of uses such as controlled drug delivery in a particular location. Both enzyme-responsive materials and hydrogels produced by using them are important for drug development. For example, peptide-based nanocapsules and nanoparticles and hydrogel based on these products are useful for the delivery of bioactive molecules due to its cleavability by protease [107, 108]. Besides this, enzyme-responsive materials and hydrogels produced by using these materials are also suitable to apply in the fabrication of smart antibacterial devices [109], where the principal idea of smart antibacterial devices is based on the release of an antibacterial agent by the presence of the bacteria themselves [5–9].

3.3 Enzyme-Responsive Hydrogels for Biocomputing

Enzyme-responsive hydrogels are useful tools for their potential applications in bio-based computing systems that have wide scale uses in biomedical applications (such as monitoring wound healing and other physiological monitoring). For example, quick and accurate detection of injury (more specifically in accidents or battle fields) is challenging which is further complicated by time and logistics required to deliver emergency medicines. In addition, injuries that cause internal bleeding (particularly, when the effected individual fails to provide any information about his own conditions due to the severity of the accident) expose terrible challenge to diagnose the exact problems, and this type of situations requires advanced diagnostic measures in order to determine the injuries to the soft tissues with a sufficient reliability. In typical cases, pieces of sophisticated diagnostic equipment are usually used to study these conditions; some examples include (a) magnetic resonance imaging and (b) electromyography, which are costly and time-consuming. Besides this, there are many issues to operate these pieces of sophisticated equipment in the actual situation when the delivery of an immediate therapeutic intervention is vitally important. Moreover, in situations where such imaging equipment or laboratory tests are unavailable or impossible to timely deliver the results, the diagnosis is generally carried out by a medical professional using different physical tests. But this technique sometimes can lead to misdiagnosis leading to inaccurate treatments that may encumber the healthcare provider with an extra burden on the patient. In such situations, effective diagnostic tools which can be reliably used to rapidly detect to devise a plausible targeted treatment are most likely to offer great promise that can

contribute to enhance the prognosis of injury (such as in accidental or battlefield conditions). Most recently, biochemical computing technology based on sophisticated enzyme-based cascades has been drawing active research interest to develop systems that can rapidly and reliably work in the diagnosis of injuries and provide useful information to prescribe appropriate emergency medicine to save lives. In this type of systems, leverage from Boolean principles is used to emulate electronic logic gates in the biochemical domain. Enzyme-based logic gates have promising capability to integrate complex patterns of biological and chemical inputs in order to provide required information for relatively rapid diagnosis on a real-time scenario. This type of advanced diagnostic systems can be engineered and leveraged to realize desired diagnosis objectives and to provide required treatment for accidental injuries in an autonomous fashion which have potentials to develop an integrated "Sense-Act-Treat" field [74, 87, 88, 106].

3.4 Smart Bandage and Wound Healing

Enzyme switchable systems have the potential for biomaterial-based display applications with potential uses in a wide range of applications including in smart bandage systems for monitoring the state of injuries and wounds. For example, switchable biomaterials such as enzyme-responsive hydrogels have the potential for producing biomonitoring devices that benefit from lightweight form factors and have the feasibility to make conformal contact with the body. Additionally, a smart bandage can be designed to detect and monitor tissue wounds in vivo, and a flexible electronic device can be used to develop noninvasive maps of pressure-induced tissue damage or even provide some information when a noticeable damage is difficult to observe visually. For example, it has been reported that by using impedance spectroscopy across flexible electrode arrays in vivo on a rat model, the frequency spectra of impedance measurements showed a correlation in a robust way with the state of the underlying tissue across multiple animals and wound types. In addition, tissue damage has also been detected by using the impedance sensor and represented visually as a wound map that helped to identify regions at risk of developing a pressure ulcer which contributed to allow intervention. So, these results illustrate the feasibility of an automated, noninvasive "smart bandage" for early monitoring and diagnosis of pressure ulcers and for improving patient care and outcomes where enzyme-responsive hydrogels can be used [87–90, 108].

3.5 Enzyme (Such as Elastase)-Responsive Hydrogel Dressing for Chronic Wounds

Chronic wounds exert an expensive economical and clinical problem by causing the deaths of millions every year where the overexpression of enzyme (such as elastase) is a main factor that prolongs the normal wound repair process within chronic wounds. Many active research groups are engaged to overcome this situation, as

for instance, specific research activities are employed for designing hydrogel-based responsive chronic wound dressing systems. In this case, polymers such as PEGA (polyethylene glycol acrylamide) in the form of particles are used to prepare hydrogels for mopping up excess elastase by exploiting polymer collapse in response to elastase hydrolytic activity within sample fluids for mimicking the environment of chronic wounds. Besides this, many other investigations have focused on the functionalization of PEGA particles by enzyme-cleavable peptides (ECPs) with charged residues in order to control polymer swelling with a consequent elastase entrapment to cause a cleavage of the charge balance changes [74, 87, 88, 110].

3.6 Complex Bioactive Fiber Systems Incorporating Enzyme-Responsive Systems by Means of Electrospinning

Enzyme-responsive hydrogels have the potentials for producing complex bioactive fibers using different techniques including electrospinning. Generally, enzyme-responsive systems have a wide range of biomedical applications including in the production of complex bioactive fibers for a variety of applications in different areas of life sciences. As for instance, the prolonged life expectancy is a direct contribution of welfare and medical developments, and this prolongation often leads to an increased physical stress on the human body that sometimes requires to replace nonfunctional and damaged tissues or organs. Artificial complex electrospun bioactive fibers have many applications in tissue engineering. During tissue engineering, in vitro cell culture is usually carried out in an artificial three-dimensional scaffold, and there are different ways of doing this. For example, modern approaches toward three-dimensional scaffolds using bioactive interfaces are frequently used in tissue engineering that also provides the opportunity to use bio-integrated and biomimetic systems. Advanced understanding on how materials passively interact or actively communicate with biological systems via designed material-biology interfaces requires precise methods for fabricating macroscopic and nanostructured materials. Recently, modern materials and technology platforms have been developed for producing bioactive scaffolds for serving a number of purposes including for providing spatial control of mechanical, chemical, and biochemical signals at the bio-interface together with the tailored pore architecture and surface topology. Enzyme-responsive hydrogels or enzyme-responsive systems can be used to establish straightforward approaches to fabricate complex structures using electrospinning in order to produce structurally and chemically bioactive fiber suitable for relatively easier cell infiltration due to the scope for a control of the mesh porosity of the electrospun scaffolds. These electrospun scaffolds also provide the scope for direct crystallization of fibers suitable to be used for the investigation of the cell ingrowth for biomedical applications. Additionally, these types of electrospun bioactive fibers can further be functionalized for the decoration of the fiber surface using biomolecules (such as peptides and sugars) or other functional materials to serve specific purposes suitable for control delivery or other related biomedical applications. Additionally, electrospun bioactive fibers have promising biomedical

applications to replicate features of the natural extracellular matrix (ECM). However, most of the electrospun scaffolds are either nondegradable or degrade hydrolytically, whereas natural ECM degrades proteolytically, often through matrix metalloproteinases (MMPs). There are reports for the synthesis of reactive macromers that contain protease-cleavable and fluorescent peptides and are able to form both isotropic hydrogels and electrospun fibrous hydrogels through a photoinitiated polymerization. In addition, biomimetic scaffolds are susceptible to protease-mediated cleavage in vitro in a protease dose-dependent manner and in vivo in a subcutaneous mouse model using transdermal fluorescent imaging to monitor degradation. This type of systems has many biomedical applications [74, 88, 95–99, 105–109].

4 Perspectives and Trends in Future Developments

One of the main strengths of enzyme-responsive materials compared to other stimuli-responsive materials clearly depends on their ability to interact with a biological environment with the same communication mechanism used by nature. In principle, enzyme-responsive materials have the ability to perform their functions with high specificity to their target enzymes. These functions are not largely undisturbed by the multitude of other processes in the biological environment. Until today, research activities on ERMs are principally aimed at developing of enzyme-responsive mechanisms and the translation into a material response. Over the last couple of decades, notable development has been realized in the form of new translational mechanisms and the incorporation of ESFs into artificial materials. Although the high attraction of enzyme-responsive systems to act dynamically and on more than one enzymatic stimulus has been recognized, this area of ERM development still holds great potential to develop new materials with unprecedented possibilities. Enzyme-responsive systems are widely studied for their potential uses in the fabrication of next-generation biological devices. For example, different areas of biomaterials widely use functionalized hydrogels for their huge potentials in different areas of biomedical applications including in cell culture [53, 54] and biosensing [55] platforms. Hydrogels are popularly used in instructive matrices for stem cell growth. In addition, the incorporation of biochemical signals that have matrix protein-specific peptidic motifs (such as fibronectin-derived arginine-glycine-aspartic acid or RGD) which can be used to facilitate cellular adhesion is particularly important. As for instance, the mechanical [57] (such as gel stiffness) and structural/topographical factors [111] of the cell-contacting matrix have special impact on biochemical signals produced from the hydrogels, and they can be regulated to control different features of hydrogels' structure in order to have control of cell fate when these hydrogels are used in cell culture or similar areas. Besides this, the preparation with particular definitions of physical characters and chemical composition may need new synthetic protocols in order to control different properties that include (a) stiffness, (b) gel network structure, and (c) chemical functionalization.

Enzymatic fabrication techniques are useful to achieve some of these goals [48, 58, 74, 87].

In addition, mimicking biological systems is a hot topic for current active research as an effort to have more decisive control over the bottom-up fabrication process. Very often different aspects of biological systems are effectively influenced and controlled using different spatially confined molecular mechanisms, some of which include (a) catalysis and (b) molecular recognition. Thus, enzymes have been used as important tools to regulate suitable nanofabrication methods with aims to develop relatively complex and highly selective next-generation biomaterials for a wide range of conventional and high-tech applications in various fields including in material and life sciences. Different important characters of enzyme-assisted formation and dismantling of supramolecular structures include (a) self-assembly under constant conditions, (b) spatiotemporal control of nucleation and structure growth, and (c) control of mechanical characters (such as stiffness). In addition, systems that assemble under thermodynamic control also show distinctive natures that include (a) defect correcting and (b) component-selecting abilities. Currently, more focus is concentrated on the effective design of suitable materials for specific applications that cover particular areas which include (a) cell culture, (b) drug delivery, (c) imaging, (d) biosensing, and (e) cell fate control. Dynamic processes in biological systems are usually controlled by enzymes. Ongoing extensive research activities aim to have better understandings of different processes at their molecular levels using enzymatic controlled self-assembly approaches. Some of the most challenging tasks in this context include (a) effectively controlling nucleation and structure growth, (b) regulating the access structures which represent non-equilibrium assemblies, and (c) producing asymmetric, dynamic, and multicomponent structures with expected functionalities and characters. An enzyme-responsive hydrogel has a wide range of continuous active research interests in order to form supramolecular structures and also to devise suitable ways to investigate the ability of these structures to perform specific activities, some of which include (a) recognition, (b) adaptation, (c) correction, and (d) interactions of the complex ways related to evolving behaviors [8, 9, 26–28, 38–41, 103–105].

5 Conclusion

Enzyme-responsive hydrogels prepared from cellulose along with other materials have suitable macromolecular networks and can work in controlled environment. An enzymatic stimulus-responsive system is a highly attractive field of research due to its many potential applications (e.g., in controlled release, drug delivery, and other areas of life and material sciences). This chapter has provided a brief overview on different selective features of enzyme-responsive hydrogels based on different polymers, and it has also stated various applications of enzyme-responsive hydrogels in specific fields including in controlled drug delivery and other areas of biomedical and material sciences. However, due to the limited scope available within the perimeter of this chapter, it is almost impossible to explain all features of different

enzymes usually used in the formulation of enzyme-responsive hydrogels. Efforts have been made to provide enough references which can be used to have more comprehensive information for advanced readers.

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Cotton Cellulose-Derived Hydrogels with Tunable Absorbability: Research Advances and Prospects

11

Yang Hu, Rohan S. Dassanayake, Sanjit Acharya, and Noureddine Abidi

Contents

Abstract

Cotton is an important, worldwide cash crop and is considered as a ubiquitous resource offering the purest form of cellulose in nature. By far, the most industrially exploited natural resources containing cellulose are wood and cotton. Cellulose derived from either wood or cotton has the same chemical structure. Hydrogels are jellylike materials consisting of substantially hydrophilic cross-linked network filled with water. Upon replacing water with air, hydrogels are able to form aerogels. Cellulose and its derivatives can be used to prepare hydrogels with tailored absorbability and adsorbability. In the first section of

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this review, we discuss recent progress in the dissolution of high molecular weight cotton-derived cellulose as the dissolution of cellulose is an important step in preparing cellulose-based hydrogels. In the second section, we focus on the preparation of various cotton cellulose-based hydrogels and their derivatives by physical, chemical, and photocatalytic processes and their current applications. The third section includes the preparation and application of cellulose-based aerogels, which are a specific dry form of hydrogels. Overall, this review covers recent research developments in cotton cellulose-based hydrogels and their broad spectrum of applications in agriculture, environment, energy, health, and medicine.

Keywords
Biopolymer · Cellulose · Hydrogel · Aerogels · Cotton

1 Introduction

Cotton is an agricultural crop that has fluffy staple fibers growing on a boll surrounding the seeds. The annual worldwide production of cotton is estimated to be 25 million tons, which makes cotton one of the leading cash crops in the world. The world's largest producer of cotton is China, while the United States of America is regarded as the largest exporter of cotton in the world [1]. Cotton fiber is almost pure cellulose, and it contains over 95% of cellulose [2]. The biological growth of cotton fiber leads to the formation of cellulose starting with the primary cell wall development after the day post-anthesis (dpa) followed by the secondary cell wall development around 21 dpa [2, 3]. The conventional textile industry mostly uses cotton fiber to manufacture a variety of textile products including clothing, terry cloth, bed clothes, upholstery, and medical gauze. Despite the very large production, the current cotton industry is facing multiple challenges due to declining market price and considerable use of regenerated cellulose fiber, rayon, and synthetic fibers such as polypropylene and polyethylene terephthalate in the textile industry. As a result, there has been an increased demand for adding value to cotton fibers by preparing novel cotton-based materials which could potentially increase profitability and competitiveness of cotton.

Gels are a solid jellylike materials with a continuous, interconnected, and three-dimensional (3D) polymeric network [4]. Hydrogels consist of hydrophilic polymeric chains and chemical groups that can hold and exchange a large amount of water with the environment [5]. When water inside the hydrogels is replaced by a continuous gas phase, hydrogels become aerogels. These aerogels exhibit a wide range of applications in oil absorbability, metal recycling, probiotics, and environmental clarification [6–8]. The most intriguing feature of hydrogels is their capability of water retention and exchange with the environment. This property makes hydrogels adaptable to many areas including industrial, agricultural, environmental, and biomedical. Recent trends indicate that hydrogels synthesized from synthetic materials are gradually becoming popular in replacing the natural hydrogels

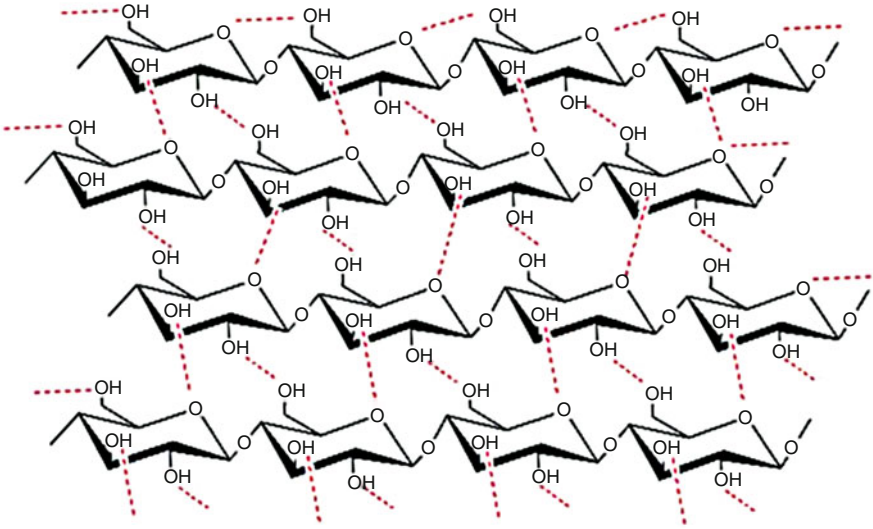

Fig. 1 Chemical structure of cellulose macromolecule with inter- and intramolecular hydrogen bonding

generated from biosynthetic polymers due to their long lifetime and more tunable capacity of water absorption. However, hydrogels prepared from biopolymers still play a pivotal role in agricultural, environmental, and biomedical areas that especially require renewability, biodegradability, and biocompatibility.

Cellulose is a carbohydrate polymer consisting of repeating β-D-glucopyranose molecules that are covalently linked through polycondensation reactions between two hydroxyl groups of two glucose units (Fig. 1), commonly known as β 1 → 4 glycosidic bond. Cellulose is found in plants, bacteria, marine animals (tunicates), and algae. Its chemical structure and composition remain unchanged irrespective of the source, while cellulose differs in its content, purity, and degree of polymerization. Wood and cotton are considered the most commercialized supplies of cellulose, while wood only contains 40% cellulose which is much lower than cotton [9, 10]. Due to the finer nanostructure, facile preparation, and broad availability bacterial cellulose has become an attractive research material in various fields [11–16]. The utilization of cellulose and its derivatives to prepare hydrogels for different applications has a long history [4]. The abundance of free hydroxyl groups in cellulose macromolecular structure allows the formation of many inter- and intramolecular hydrogen bonds and the semicrystalline structure makes cellulose highly reactive for advanced functionalization for superabsorbent hydrogels [17, 18]. Most of cellulose-based hydrogels are prepared from bacterial cellulose, wood cellulose, and its derivatives. However, only a few studies have been reported on the use of cotton cellulose for preparing hydrogels. This could be due to the fact that (1) cotton fiber almost entirely goes to traditional textile processing; (2) the difficulty in dissolution of cotton cellulose, and (3) most of the cellulosic materials available in the market

are derived from wood. Cotton cellulose has a high degree of polymerization (DP) (10,000–15,000) which makes it much harder to dissolve as compared to wood cellulose which has a relatively low DP (~300–1700) [9, 19–21].

This review discusses up-to-date research advances on the cotton cellulose-based hydrogels with tunable absorbability. Since the preparation of cellulose-based hydrogels involves cellulose dissolution, the first section of this review is focused on the dissolution of cotton cellulose and its derivatives. A diverse range of applications of cotton cellulose-based hydrogels is also discussed. The final section focuses on cotton cellulose-based aerogels and their current uses.

2 Dissolution of Cotton Cellulose and Its Derivatives

Most of the reported dissolution processes of cellulose carry limitations such as low cellulose solubility in terms of molecular weight and concentration, volatility, high cost, poor solvent recovery, high processing temperature, process instability, and environmental concerns [22]. Two industrial processes, viscose and lyocell, use raw cellulose derived mostly from wood pulp to produce regenerated fibers [23]. These industrial processes can also be applied to cotton cellulose, although cotton cellulose is not a popular feedstock to produce regenerated fibers [24]. Both viscose and lyocell processes are associated with several issues, such as generation of highly toxic carbon disulfide (CS_2), heavy metal compounds, hazardous by-products, unwanted side reactions, and harsh dissolution conditions [9, 25, 26].

2.1 Cotton Cellulose

Cellulose derived from wood remains the main source for the preparation of regenerated materials such as fibers and films in the industry [27]. However, the dissolution of cellulose from other sources including cotton has been investigated in numerous solvents along with the preparation of regenerated materials such as fibers, hydrogels, and aerogels [27–41]. Unlike other cellulose sources, native cotton cellulose is obtained in the form of fibers, which can be directly processed into yarn. However, a significant amount of cotton fibers is discarded as waste during ginning and carding processes. Therefore, there is a need to utilize the waste cotton as a source of cellulose to prepare various regenerated materials.

Cotton contains the purest cellulose among almost all other sources as shown in Table 1. The DP of cellulose varies upon the source and is described in Fig. 2 according to the type of extraction and purification. The cellulose content in cotton can reach over 99% after scouring and bleaching processes that remove non-cellulosic materials such as waxes, pectin, proteins, and inorganics. The DP of cotton cellulose in the natural state is higher than 10,000, while it is reduced to 1000–3000 or less in the preparation of cotton linters and cotton linter pulp [20]. Due to the high molecular weight, complex polymeric network, and non-covalent interactions among molecules, cellulose is generally inert to mild chemical

Table 1 Cellulose, hemicellulose, and lignin contents in wood and common agricultural residues [12]

Lignocellulosic materials	Cellulose, %	Hemicellulose, %	Lignin, %
Hardwood stems	40–55	24–40	18–25
Softwood stems	45–50	25–35	25–35
Cotton seed hairs	80–95	5–20	0
Nut shells	25–30	25–30	30–40
Corn cobs	45	35	15
Grasses	25–40	35–50	10–30
Paper	85–99	0	0–15
Wheat straw	30	50	15
Leaves	15–20	80–85	0

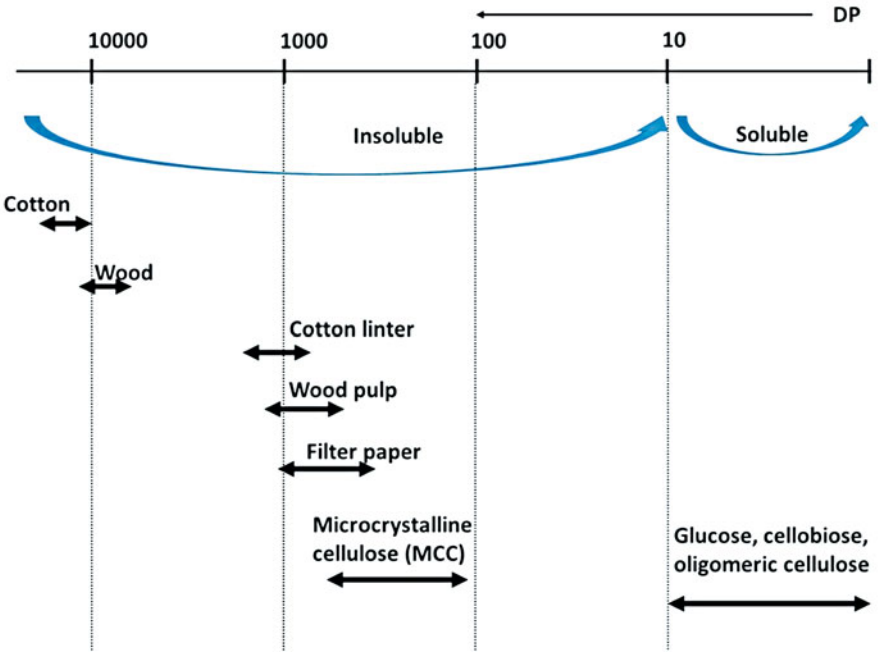

Fig. 2 Typical DP values of different cellulose substrates and their solubility [20]

processing. Therefore, it is hard to dissolve cotton cellulose in water and common solvents under mild conditions. The preparation of hydrogels generally requires the dissolution of cellulose as the first step to obtain homogeneous cellulose followed by mold casting and regeneration to obtain final hydrogel products [10]. Homogeneous dissolution of cellulose prior to the synthesis of hydrogels is required in order to achieve the desired homogeneous structure and superior features [26, 42].

Cost-effective and environmentally benign cellulose dissolution, in general, remains a challenge owing to its high molecular weight and high structural order.

The problem becomes more complicated with cotton cellulose because it possesses high molecular weight and structural order (high amount of crystalline cellulose) among all plant cellulose macromolecules. Since the molecular weight of a polymer is a key parameter in determining its solubility and is inversely related to the entropic driving force which contributes to the dissolution, cotton cellulose of high molecular weight inherently presents a low solubility [43]. Numerous studies have focused on both fundamental and applied aspects of cellulose dissolution. The majority of studies available in the literature use wood-based cellulose including microcrystalline cellulose (MCC) and wood pulps, which are different from cotton cellulose in terms of both molecular weight and crystallinity. These studies showed that different regenerated cellulose materials such as rayon and lyocell can be prepared from cellulose solution using different solvents [44, 45]. Since solvents effective for low molecular weight cellulose are not efficient on high molecular weight cellulose such as cotton under similar processing conditions, only few studies were focused on the dissolution of cotton cellulose in common cellulose solvents [46]. Decreasing the molecular weight of cotton cellulose by means of chemical and enzymatic pretreatments could enhance the solubility of cotton cellulose. Other pretreatments which facilitate the dissolution of cotton cellulose include treatment with sodium hydroxide, solvent exchange with acetone, and freeze-drying processes [10, 46, 47].

2.2 Dissolution of Cotton Cellulose in Different Solvents

2.2.1 Viscose Process

The "viscose" process ($NaOH + CS_2$) is the most dominant process employed by the industry to dissolve cellulose and produce commercially available regenerated cellulosic materials, such as rayon and cellophane [48, 49]. In the industry, high purity dissolving pulp is mostly derived from wood; only 10% of the dissolving pulp is produced from cotton [50]. In a typical viscose process, cellulose is steeped in sodium hydroxide solution to obtain an activated cellulose called soda cellulose, in which one of the three reactive hydroxyl groups on each glucose unit of cellulose is replaced by sodium ions. Then, the soda cellulose is mixed with carbon disulfide (CS_2) to obtain cellulose xanthate, derivatized cellulose. Cellulose xanthate is soluble in aqueous sodium hydroxide and can form "viscose" solution. Then in the coagulation bath, cellulose xanthate is converted back to cellulose in the shape of filaments and films from the "viscose" solution [9, 51, 52]. Studies were focused on new strategies to reduce the environmental impacts of the viscose process. Enzymatic pretreatment of cellulose (dissolving pulp) with endoglucanase and xylanase was reported to increase the reactivity of the dissolving pulps, and thereby the consumption of CS_2 can be reduced by 30% [53, 54]. Mechanical pretreatments such as grinding and PFI refining of cellulose were reported to enhance the reactivity of cellulose pulp in the viscose process [55]. The modified viscose process generates a soluble derivative called cellulose carbamate that is soluble in aqueous NaOH. Carbamate process is deemed more environmentally friendly as compared to the viscose process [9, 25, 30, 56] (Fig. 3).

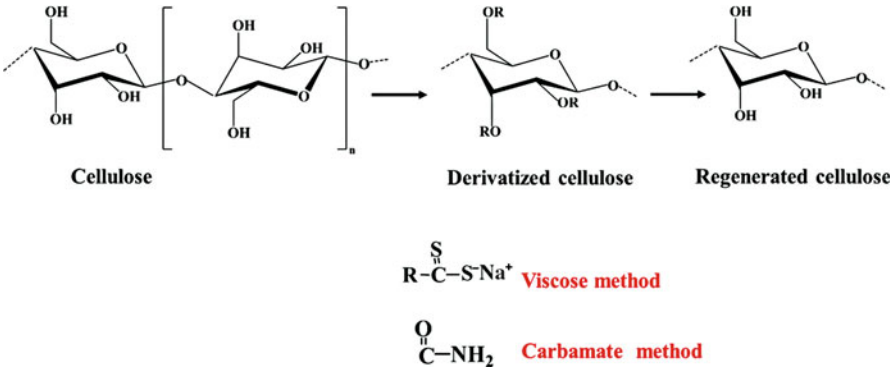

Fig. 3 Process principles in viscose and Carbamate processes [9]

Few studies were focused on the improvement of carbamate process using cotton linter cellulose. Yin et al. optimized the carbamation of cotton linter cellulose (DP ~520) with the aid of CO_2 supercritical dehydration of cellulose [57]. The study showed that CO_2 supercritical dehydration could yield cellulose carbamate of high nitrogen content, which positively correlates with the solubility of cotton cellulose in aqueous NaOH. In addition, the pretreatment of cotton linter cellulose (DP ~550) by means of microwave heating at 255 W for 2–5 min under catalyst-free and solvent-free conditions was conducive to the enhancement of nitrogen content of cellulose carbamates from 0.651% to 2.427% [58]. Fu et al. further optimized the carbamate process by improving the stability of the dissolved carbamate solution of cotton cellulose (DP ~790) by adding a small amount of ZnO in NaOH during the dissolution using conventional viscose method [56].

2.2.2 Aqueous Alkaline Systems

The potential of aqueous bases as cellulose solvents was reported as early as 1930, and it has been extensively studied since then [42, 47, 59–63]. Low molecular weight cellulose below 268,000 can be partially dissolved in aqueous NaOH of 7–10% concentration [64]. The formation of NaOH hydrates in water is the major driving force to break down the intra- and intermolecular hydrogen bonding of cellulose [65]. This system offers many advantages because of its low cost, minimal environmental issue, common chemicals, and facile dissolving process. However, NaOH/water system is unable to completely disrupt the semicrystalline region of cellulose, and the solubility is limited to cellulose of relatively low molecular weight. The improvement of cellulose dissolution in this system includes mechanical/physical, chemical, and enzymatic pretreatments of cellulose. Ball milling and steam explosion followed by grinding of wood cellulose pulp have been reported to enhance the solubility of cellulose in this system [47, 66]. Enzymatic pretreatments of cotton linter cellulose (DP ~850) could remarkably increase the solubility of cotton linter cellulose from 30% to 60% and significantly decrease the dissolution time [66]. Additionally, the use of additives in NaOH/water solvent

system, such as thiourea, urea, and polyethylene glycol, has been reported to enhance the dissolution ratio and the stability of the cellulose solution [28, 67–70]. For example, NaOH/ urea system was used to dissolve relatively high MW cotton cellulose (DP ~620) within 30 min at a concentration of 4.5% urea in NaOH [44]. Other bases, such as LiOH, KOH, and quaternary ammonium hydroxides, can also be used instead of NaOH to work with the additives to dissolve cellulose [48, 71–73]. One study reported that LiOH/urea/ H_2O system was more effective than NaOH/urea/H_2O system [28].

2.2.3 DMAc/LiCl System

N,*N*-dimethylacetamide (DMAc) combined with lithium chloride (LiCl) is a common and powerful solvent system for the dissolution of cellulose [74–76]. LiCl (8%) in DMAc (w/w) has been widely used. An activation procedure or a pretreatment is usually required especially for high MW cellulose such as cotton cellulose. The typical activation method involves solvent exchange where cellulose is first treated either in water, liquid ammonia, or NaOH, and then the solvent is exchanged to methanol, ethanol, or acetone to finally (dry) DMAc [77]. Heating or refluxing cellulose in DMAc or DMAc/LiCl has also been proposed to activate cellulose for better dissolution [78]. Although different mechanisms of cellulose dissolution in DMAc/LiCl solvent system have been proposed, most authors believe that the formation of Li^+[DMAc] macrocation is the driving force for the dissolution of cellulose where DMAc is considered a strong Lewis base and Li^+ is highly oxophilic cation [77, 79–83]. The native hydrogen bonding in cellulose is disrupted once the free Cl^- ions form hydrogen bonds with OH groups of cellulose in addition to the weak dipole-dipole interaction of macrocation via Li^+ with cellulose molecules (Fig. 4) [26, 76, 77, 84, 85]. A drawback of DMAc/LiCl solvent system is that a serious degradation of cellulose (loss of molar mass) may occur during the dissolution process by forming reactive intermediates at elevated temperature (>80 °C) [86].

2.2.4 Lyocell Process

Amine oxides constitute another important class of non-derivatizing cellulose solvents [87]. Among the amine oxides, *N*-methylmorpholine-*N*-oxide monohydrate

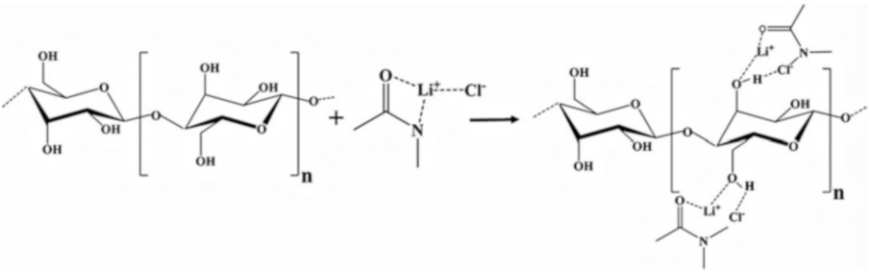

Fig. 4 Schematic of proposed hydrogen-bond breaking mechanism for cellulose dissolution in DMAc/LiCl [25]

(NMMO) is considered the superior cellulose solvent. The lyocell process is based on the use of NMMO as a solvent for cellulose. NMMO monohydrate at 13% concentration in water can dissolve cellulose without derivatization to achieve a solubility of 23% cellulose concentration at 80–120 °C [9, 88]. The mechanism of NMMO to dissolve cellulose is due to the formation of one or two hydrogen bonds between the oxygen of NO group and hydroxyl groups of cellulose caused by the strong dipolar character of the NO group [74, 87]. Lyocell offers several advantages over industrially predominant viscose process. It can directly dissolve cellulose in NMMO without extra activation and pretreatment. It does not need an intermediate transfer to cellulose derivatization, and it significantly shortens the production route and also eliminates the release of highly toxic CS_2. Additionally, the industrial recovery of NMMO can be as high as 99.7% [9]. Lyocell fiber also has advantages over rayon in many respects such as its strength in both wet and dry states, modulus of elasticity, absorbable behavior, gloss, and touch. However, the lyocell process suffers from some drawbacks including unstable regenerated fiber, unwanted side reactions, and excessive degradation [9]. Therefore, strategies have been applied to optimize the stabilization of the reaction and reduce the occurrence of unwanted side reactions [89].

2.2.5 Ionic Liquids

Ionic liquids (ILs) have emerged as promising non-derivatizing cellulose solvents with high potential to dissolve cellulose. ILs are generally asymmetrical organic salts that remain liquid at relatively low temperature (<100 °C). An IL usually consists of a bulky low charge density organic cation and a low charge density inorganic or organic anion [90–92]. Swatloski and coworkers first reported several ILs capable of dissolving cellulose, and a large variety of ILs has been developed and specifically applied to the dissolution of cellulose since then [90, 93, 94]. ILs exhibit many advantages over other cellulose solvents such as thermal and chemical stability, negligibly low vapor pressure, high efficiency of cellulose dissolution, and recyclability. In addition, a large variety of possible ion combinations allows tailoring ionic liquid solvents with specific properties for specific purposes. The number of potential ion combinations available is estimated to generate 10^{12} of ILs [93, 95]. The most efficient ILs reported for the dissolution of cellulose are mainly composed of a salt with halide, phosphonate, formate, or acetate as an anion and imidazolium, pyridinium, choline, or phosphonium as a cation [96–103]. As compared to NMMO and DMAc/LiCl, ILs have exhibited a capability of dissolving high molecular weight cotton linter (DP ~4745) [96]. Some cellulose pretreatments, such as mechanical ball milling, ethanol treatment, ultrasonic irradiation, and microwave irradiation can promote the dissolution of cellulose [104]. The dissolution of cellulose in ILs depends on the disruption of hydrogen bonding of cellulose chains by both anions and cations from ILs (Fig. 5). Anions and cations play a significant role during the dissolution. For example, imidazolium-based ILs dissolve cellulose by means of interaction of hydrogen bonding between the anions of the ionic liquid and the hydrogen of the C3...OH and C6...OH groups in cellulose. Meanwhile, acidic protons of the cations, especially the H2 proton in the imidazolium ring of the cation,

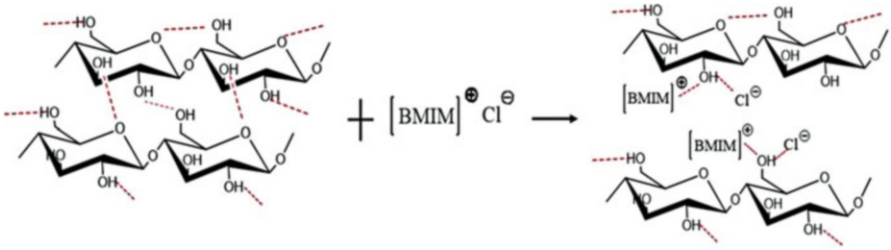

Fig. 5 Proposed cellulose dissolution mechanism in 1-butyl-3-methylimidazolium chloride [95]

form hydrogen bonding with the oxygen at C2. . .OH and the ring oxygen (O5) of cellulose [95, 105, 106]. Despite the great potential of ILs as cellulose solvents, ILs have not been applied to industrial applications yet. High production cost, high viscosity, high hygroscopic property, and reduction in dissolution ability and processing difficulties due to long-term dissolution are drawbacks of ILs [26, 107]. Efforts have never been stopped for exploring new ILs and improving the process of ILs to dissolve cellulose. A recently synthesized ionic liquid, 1,5-diaza-bicyclo [4.3.0]non-5-enium acetate ([DBNH][OAc]), was employed in the development of a process called Ioncell-F to produce regenerated cellulose fiber with properties comparable to lyocell [44, 45].

2.3 Other Methods for Preparing Cellulose-Based Hydrogels

Other methods for preparing cellulose-based hydrogels consist of synthesizing water-soluble cellulose derivatives and then forming hydrogels by means of physical, chemical, and radical cross-linking. Water-soluble cellulose derivatives contain methyl cellulose (MC), carboxymethyl cellulose (CMC), hydroxypropyl cellulose (HPC), and hydroxypropyl methylcellulose (HPMC) [4]. Generally, water-soluble cellulose derivatives have a low molecular weight (DP $<$100), and the substitution of hydroxyl groups on the cellulose macromolecular chain is more than 1.0 degree of substitution (DS) [9, 108]. These features make water-soluble cellulose derivatives quite easy to dissolve in water and other common solvents to prepare hydrogels. Most of water-soluble cellulose derivatives require that cellulose be well-dissolved or swollen prior to the modification, and they are produced from cellulose derived from wood because of the low molecular weight and abundant commodity of wood cellulose available. However, a few studies use cotton cellulose derived from waste cotton fabric, cotton by-products, and absorbent cotton that present low molecular weight to synthesize water-soluble cellulose derivatives [109–111].

Physical cross-linking is not involved in the covalent bonding. Cellulose derivatives are simply dissolved in water at a relatively high concentration under different conditions (heat or stir) to form hydrogels by means of ionic bonding, hydrogen bonding, and molecular interaction between polymeric chains [112–114]. Chemical and radical cross-linking of cellulose derivatives to form

hydrogels are achieved through covalent bonding by functionalized cross-linker or self-induced bonding by light, heat, and pressure [115, 116]. For example, cellulose from cotton waste textiles was carboxymethylated and cross-linked by divinyl sulfone to form superabsorbent hydrogel using NMMO to dissolve cellulose. The resulting CMC products exhibit a high binding capacity of 541 g/g and a rapid absorption rate within 60 min when the sample is immersed in water [117].

3 Applications of Cotton Cellulose-Based Hydrogels

Most of cellulose-based hydrogels have been used in agricultural, environmental, health, and medical areas depending on their super-absorbability and tunable absorbency. Cotton cellulose is not the major feedstock for making hydrogels, and only cotton cellulose products, including linter, linter pulp, and waste with low molecular weight, have been explored to prepare various hydrogels for diverse applications. This review discusses only the applications of hydrogels derived from cotton cellulose.

3.1 Applications in Agriculture

Superabsorbent hydrogels with self-tunable absorbency have been used in agriculture as soil additives or water reservoirs to meet the requirement of reducing water consumption and optimize the utilization of water resources [118]. Synthetic polymers such as sodium polyacrylate exhibit excellent water retention and discharge under specific conditions. However, they are not biodegradable or degrade too slowly, which may affect the overall soil quality [119]. Cellulose and its derivatives have an advantage over synthetic polymers due to their biodegradability and biocompatibility. The natural degradation of cellulose-based hydrogels in the soil could be a nutrition source for most plants. For example, during the whole lifetime of hydrogels, hydrogels are first able to store water from the environment when a rain event occurs and switch the appearance of hydrogels from glassy to a rubberlike state. The water discharge occurs when the soil dries and the rate of water release from the hydrogels can be controlled by controlling the functional groups of cellulose-based hydrogels [120]. A typical illustration is shown in Fig. 6 demonstrating the process of restoring and discharging water periodically fulfilled by cellulose-based hydrogels. The large-granule cellulose gel shown in Fig. 6 is better than the fine-granule gel because larger-granule gel can maintain better soil porosity that allows the air to flow. Water and nutrients can also permeate the thick soil layer and diffuse well around the root.

There are only a few examples using cotton cellulose to prepare hydrogels as soil additives for adjusting water requirement. Kono and coworker reported a superabsorbent hydrogel prepared from cotton cellulose with a high DP of 2400 [121]. The authors used LiCl/*N*-methyl-2-pyrrolidone (LiCl/NMP) to dissolve cotton cellulose followed by esterification of the dissolved cotton cellulose using 1,2,3,4-butanetetracarboxylic dianhydride (BTCA). Then the esterified product was

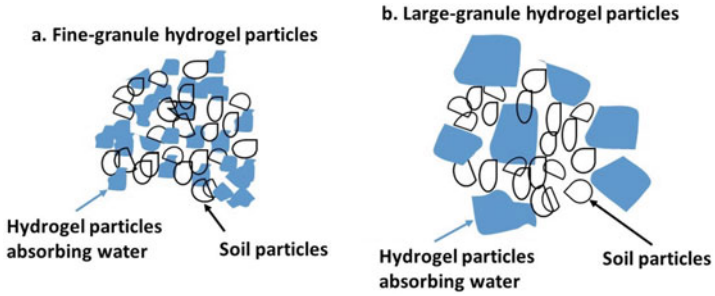

Fig. 6 Cellulose-based hydrogels: (**a**) fine-granule gel and (**b**) large-granule gel [120]

converted to sodium carboxylates in aqueous NaOH. The final hydrogel product demonstrates its potential in water retention and discharges in the soil with an excellent absorbency of 720 times of its dry weight and a good biodegradability. Cross-linked CMC prepared from cotton linter pulp and cross-linker (epichlorohydrin) was also reported [122]. Cotton linter was first swollen and then carboxymethylated followed by cross-linking. The resulting cross-linked CMC hydrogel exhibited an improved swelling behavior, which is sensitive to a change in the pH variation. This hydrogel may satisfy different soil pH requirements under different environments.

3.2 Environmental Applications

Cellulose-based hydrogels as pollutant adsorbents can remove heavy metal ions, dyes, and pesticides from water [123]. The absorbency of cellulose-based hydrogels can be easily tailored by using different cellulose derivatives. For example, cellulose grafted with acrylonitrile is a good adsorbent of Cr^{5+}, and oxidized cellulose-based hydrogel is considered a good absorbent for Hg^{2+} with an adsorption capacity of 258.75 mg/g at 30 °C and pH 4.0 [124]. The preparation of hydrogels from these cellulose derivatives requires the dissolution of cotton or wood cellulose, modification of cellulose by specific functional groups, and then formation of hydrogels by means of physical or chemical cross-linking. In addition, hydrogel composites prepared from cotton cellulose and functional additives also play a role in the removal of heavy metal ions. Zhou and coworkers developed a fixed-bed column filled with cellulose/chitin hydrogel beads for the removal of a number of heavy metal ions in a broad range [125]. A mixture of 4% cellulose solution prepared in DMAc/LiCl and 2% chitin solution prepared in NaOH/thiourea was used to coagulate and prepare composite hydrogel beads. The assembled bed with hydrogel beads could perform four cycles of adsorption/desorption to reach an adsorption efficiency of Pb^{2+} more than 70%. The cellulose/chitin beads also exhibited an excellent recycling capability. Beads treated with 0.1 M HCl can restore the regeneration efficiency up to 99%.

The removal of dye and pesticides can be achieved using cellulose-based hydrogel prepared from cotton cellulose modified with functional groups to synthesize super-adsorbent hydrogels or cellulose nanocrystals (CNCs) hydrogel composites. Zhou and coworker synthesized a super-adsorbent cellulose-graft-acrylic acid hydrogel using commercial cotton linter powder for the removal of methylene blue (MB) dyes from wastewater [126]. The resulting hydrogels exhibited excellent MB adsorption capacity of 2197 mg/g, and nearly 70% MB in weak acid solution could be removed during the desorption process. In addition, CNCs/alginate hydrogels beads were used for MB removal up to 97% efficiency [127], as well as CNCs-reinforced polyacrylamide-methylcellulose hydrogels were found highly effective for agricultural applications as an adsorbent for insecticides or as a carrier for agrochemical controlled release [128].

3.3 Applications in Health and Medicals

Cotton cellulose has a long history of application in health and medical areas. A great amount of traditional medical gauze tape and bandage is employed every day in hospitals, although modern gauze tape made of synthetic fibers gradually becomes popular due to its versatile properties such as self-adhesion and antibacterial. Therefore, it is not necessary to dissolve cotton cellulose to prepare cellulose-based hydrogels for this type of applications. However, when advanced applications are required, such as diapers and wound healing contact films, cellulose-based hydrogels are required. Two kinds of cellulose samples including cotton linter pulps and wood pulps are the major feedstock needed for the preparation of cellulose-based hydrogels [129] for health and medical uses. Diapers were the first cellulose-based super-absorbent, initially used in the healthcare industry in 1982 in Japan [120]. They were made from cellulose acrylate which is mostly used as a major functional compound in disposable diapers [130]. In recent years, a new generation of diapers with advanced functions has emerged. Peng and coworker synthesized multifunctional cellulose-based superabsorbent hydrogels by means of cross-linking and quaternization of cellulose in NaOH/urea solution [129]. The resulting hydrogel exhibited a high swelling ratio of 984 g/g and a good antimicrobial property against *Saccharomyces cerevisiae*.

Regarding wound healing and drug delivery, cellulose-based hydrogels play a key role as well. In addition to the traditional use as wound dressing materials, regenerated fibers made of cotton cellulose solution can be obtained by means of electrospinning or wet-spinning approaches. Various modifiers and chemicals can be added during the regeneration of dissolved cotton cellulose to exhibit versatile features of liquid exchange and drug delivery [131]. Further research reported that functionalized cellulose-based hydrogels may work as a temporary skin substitute to compensate the dysfunction of wound tissue, such as providing moisture to wound bed, as well as absorbing wound exudates [132, 133]. However, due to its non-biodegradation in the body, cellulose-based hydrogels are constrained to the long-term use as skin substitutes for chronic wound healing (e.g., second-degree

burn and above). Hu and coworkers performed considerable work to prepare cellulose-based hydrogel bioabsorbable by means of enzymatic incorporation to cellulose-based hydrogels [12, 134]. For drug delivery, a superabsorbent hydrogel synthesized from cotton cellulose and succinic anhydride exhibited an excellent water retention capacity of 400 times its dry weight [111]. This hydrogel can be degraded completely after 25 days, which is a good candidate for a drug carrier vehicle to transfer and release effective ingredients in the body.

4 Cotton Cellulose-Based Aerogels

Aerogels are organic, coherent, highly porous, spongelike, or skeleton-like solid materials formed by the solidification of a colloidal gel network followed by replacing the liquid in the gel with one continuous gas or air [135, 136]. Generally, the preparation of aerogels is completed by removing the liquid from a hydrated interconnected gel network to leave a gaseous phase via freeze-drying or supercritical drying operations, and inversely the process of reabsorbing the liquid makes the aerogels become hydrogels again [135, 136]. When the liquid in the gel is water, aerogels may be deemed as pre-hydrogels. Most of the hydrogels require dehydration or remain a low hydrous level materials to ensure the best absorbability of liquids. Of course, some hydrogels need to maintain a high hydrous level to discharge the desired liquids to the environment, such as hydrogels used for wound healing that require keeping the wound moisture for tissue cell growth [12, 133]. Therefore, this section describes aerogels with super-absorbability and tunable absorbency.

Cellulose-based aerogels possess diverse characteristics including ultralight weight, high internal surface area, 3D porous structure, low density, high rigidity, low dielectric permittivity, and thermal conductivity [137, 138]. Cellulose aerogels are usually prepared from long-chain fibers and their depolymerized forms. The depolymerized forms of long-chain cellulose fibers are mainly microcrystalline cellulose (MCC) and nanocrystalline cellulose (NCC). Acid hydrolysis of native long-chain cellulose fibers derived from wood, cotton, and bacteria can yield low molecular weight cellulose products like MCC and NCC with a DP of 100–1000 [9, 139–142]. Cellulose aerogels prepared from NCCs have attracted special interest due to their enhanced mechanical performance with high axial Young's modulus in the range of 110–220 GPa [143]. NCC can also be used to prepare aerogels with ultralow densities below 5 mg/cm^3, exceptionally high 3D nanostructured porosity in excess of 99%, and high internal surface areas [144]. Figure 7 shows a digital photograph and a scanning electron microscopic (SEM) image of cotton cellulose-derived monolithic nanoporous aerogels. Over the past few years, cellulose-based aerogels have been considered for diverse applications including wastewater treatment and dye removal [6, 126, 145], membranes [146–148], biomedical [148, 149], gas adsorption [150], energy absorbers [151, 152], oil sorbents [153, 154], insulation materials [152, 155], and supercapacitors [156, 157].

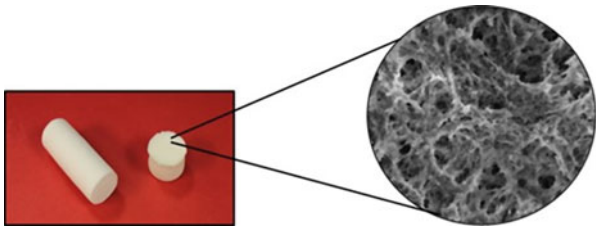

Fig. 7 Digital photograph of cotton cellulose-derived monolithic nanoporous aerogels. (Inset: SEM image of the aerogel at a magnification of 500 nm)

Although cotton contains over 90% of cellulose, there is a scant information in the literature about the uses of cotton cellulose-based aerogels. In this section, we report on the preparation of cotton cellulose-based aerogels and their current applications.

4.1 Preparation of Cotton Cellulose-Based Aerogels

The preparation of cotton cellulose-based aerogels involves five main processes: scouring and bleaching, dissolution, gelation, regeneration and solvent exchange, and dehydration. Scouring and bleaching processes remove noncellulosic materials including pectin, wax, lignin, hemicellulose, and pigments of cotton. The next step is the dissolution of pure cotton cellulose in a suitable solvent. This cellulose solution can be used to cast materials with different shapes such as films, fibers, monoliths, films, or dense powders. Then, the gelation process is facilitated at higher temperatures (50–60 °C) where the particles dispersed in the solution evolve to form a continuous three-dimensional (3D), interconnected, rigid, wet gel-like polymer network extending throughout the solution. The regeneration and solvent exchange step lead to the hydration of gels. This step involves the immersion of the cellulose gel solution in a coagulating bath and frequent replacement of the coagulating bath until the solvent exchange is complete. The final drying step is the removal of solvent inside the hydrated gels without any structural collapse. Figure 8 shows the general schematic representation of the preparation of cellulose aerogels from raw cotton.

4.2 Applications of Cotton Cellulose-Based Aerogels with a Good Absorbency

4.2.1 Oil and Solvent Spillage Cleanup

Oil spillage has become a serious environmental concern worldwide due to the rapidly increasing use and transportation of oils and accidental oil leakage and spillage. Those spillages can cause severe pollution of natural water resources including underground water streams and coastal waters and consequently affecting both human and animal health. Currently used technologies for the removal and separation of oil spillage include chemical treatments [158], bioremediation [159],

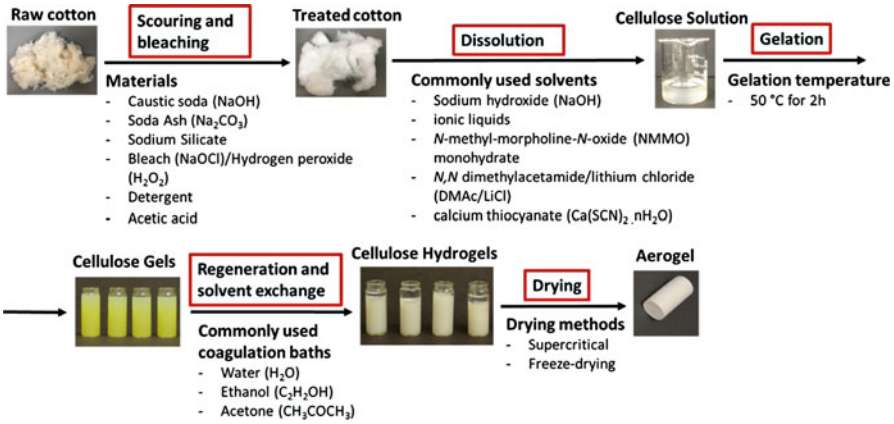

Fig. 8 Schematic illustration of the preparation of cellulose aerogels from raw cotton

and physical methods [160]. Among these, adsorbents used in physical methods are considered as one of the most efficient and effective approaches. Recently, cellulose-based aerogels have been investigated as suitable sorbents for removal of oil due to their natural abundance, sustainability, low cost, and environmental benignity. Cheng and coworkers reported on the utilization of pure cotton aerogels and cotton cellulose aerogels derived from pure cotton and cellulose fiber from paper waste for the adsorption of oil and organic solvents [161]. Cotton cellulose-based aerogels showed a better performance over pure cotton aerogels because of the synergistic effects of two different cellulose fiber sources. The adsorption capacity of the composite aerogel is 72.3 and 94.3 g/g for machine oil and dichloromethane, respectively. Wan et al. investigated the waste motor oil adsorption capacities of cotton cellulose-based aerogels modified by methyltrichlorosilane (MTCS) [162]. These MTCS-modified cotton cellulose aerogels exhibited an adsorption of approximately 14 times of its dry weight. Wang and coworkers also demonstrated the adsorption of diesel oil onto cotton-derived carbon fiber aerogels grafted with nitrogen-doped graphene [163]. Bi et al. investigated the adsorption of oil and organic solvents onto aerogels prepared from twisted carbon fibers (TCF) derived from cotton fibers [164]. They reported adsorption capacity in the range of 50–190 times the initial weight of TCF aerogels with excellent reusability.

4.2.2 Removal of Organic Pollutants and Heavy Metals

With the rapid industrialization and urbanization, a variety of industrial effluents containing organic and inorganic pollutants are discharged into natural water supply. Among those, pollutants such as organic dyes and heavy metal ions are extremely stable and persistent environmental contaminants and could not be eliminated naturally. Therefore, these pollutants pose a major threat to human health as well as aquatic ecosystems. Different approaches including chemical precipitation and adsorption, advanced oxidation and reduction, biological degradation, coagulation

and flocculation, membrane separation, ultrafiltration, and photocatalytic and sonochemical degradation have been employed for the removal of organic dyes and heavy metals [165]. The adsorption technique is considered to be the most efficient physiochemical approach due to its low operation cost and simplicity. Cellulose-based aerogels have been extensively investigated as adsorbents for the removal of organic contaminants and heavy metals. Chen and coworkers studied the removal of organic pollutants (phenol (PhOH), aniline ($PhNH_2$), methyl orange (MO), methylene blue (MB), rhodamine B (RhB), and Victoria blue (VB)) and heavy metal ions (Pb^{2+}, Co^{2+}, Cd^{2+}, and Sr^{2+}) using cotton-derived porous carbon (CDPC) and cotton-derived porous carbon oxide (CDPCO) aerogels [166]. They reported maximum adsorption capacity of 1519 and 1020 mg/g of MB for CDPC and CDPCO. The maximum Pb^{2+} adsorption of 111.1 and 21.2 mg/g was achieved for CDPC and CDPCO, respectively. Li et al. showed the maximum monolayer methylene blue (MB) adsorption of 101.23 mg/g for carbon fiber aerogels prepared from waste cotton [167]. Zhou et al. reported maximum MB adsorption capacity of 2197 mg/g for cellulose-graft-acrylic acid (C-g-AA) hydrogels derived from cotton linters [126]. Melone and coworkers reported on the preparation of ceramic aerogels via one-pot method by mixing aqueous hydrogels of cotton cellulose with titanium dioxide (TiO_2) or TiO_2/silicon dioxide (SiO_2) solutions and subsequent freeze-drying [168]. The calcined ceramic aerogels showed pronounced adsorption and photodegradation efficiency toward MB and RhB dyes.

4.2.3 Energy Storage and Carbon Dioxide Adsorption

The development of energy storage systems such as batteries and supercapacitors has continued to evolve over the last few years due to the variable production of energy from some renewable energy technologies. The energy storage systems have great potential for providing a stable energy supply and ensuring that the supply of energy matches the demand. Recently, supercapacitors have been developed as one of the most promising energy storage devices for their faster charge-discharge rates, excellent stability and cyclic retention, higher power, and minimal charge separation. Carbon materials such as graphene, activated carbon, carbon nanotubes, and carbon aerogels have been broadly used in supercapacitors [169, 170]. Carbon aerogels have advantages over other carbonaceous materials, including high surface area and porosity, excellent electrical conductivity, and high chemical and mechanical strength. Carbon aerogels derived from cotton cellulose have also been investigated for high-performance supercapacitor applications. Hu et al. reported the supercapacitance of 225 F/g and excellent cycle life with 94% of capacitance retention after 5000 charge/discharge cycles for nitrogen-doped carbon aerogels prepared from cotton linters and ammonia as a nitrogen source [171]. They also reported CO_2 gas adsorption of 4.99 mmol/ g for their material. Nitrogen-doped graphene aerogels prepared from raw cotton and urea showed a specific supercapacitance of 107.5 F/g [163]. Tian and coworkers investigated the super capacitance properties of silver (Ag)/polyaniline (PANI)/cellulose aerogel nanocomposite prepared from cotton linter pulp [172]. They reported a specific capacitance of 217 F/g with capacitance retention of 83% after 1000 cycles.

4.2.4 Biomedical

Owing to their high surface area and porosity, interconnected 3D network, biocompatibility, biodegradability, relative abundance, and cost-effectiveness, cellulose aerogels have attracted tremendous attention in a variety of biomedical applications. The applications of cellulose aerogels include tissue engineering, biosensors, antimicrobial agents, ultrasound contrast agents, drug delivery, and disease diagnosis [173]. However, the use of cotton-derived cellulose aerogels in biomedical field has not been fully explored. Wansapura et al. reported on the preparation of cotton cellulose-cadmium-tellurium quantum dot aerogels and its antibacterial activity against gram-positive bacteria, *Streptococcus aureus* [174]. Edwards and coworkers reported on the utilization of nanocellulose aerogels in biosensing of proteases [175, 176]. They prepared peptide-nanocellulose aerogels (PepNA) derived from cotton as biosensors for detecting proteases and reported the detection sensitivity of 0.13 units/mL for human neutrophil elastase.

5 Conclusion and Prospects

Cotton is a worldwide industrial crop which inherits the purest form of cellulose in nature. Most of harvested cotton goes to textile industry to produce fabrics for clothing, tablecloth, medical gauze, and home decoration. Compared to wood cellulose, it is uncommon to use cotton cellulose as a major feedstock to produce hydrogels. Because cellulose dissolution is a prerequisite to prepare regenerated cellulose materials, the high molecular weight and high crystallinity combined with extensive hydrogen bonding of cotton cellulose are the major obstacles for converting cotton cellulose to hydrogel materials. New emerging solvents can effectively dissolve cotton cellulose which can subsequently be converted to various materials including cellulose hydrogels. This review summarizes the current research trends in cotton cellulose-based hydrogels with tunable absorbability and cotton cellulose-based aerogels and their diverse range of applications in agriculture, environment, energy, health, and medical fields.

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Adsorption Mechanism of Cellulose Hydrogel by Computational Simulation

12

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Contents

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Abstract

In this chapter, different adsorption mechanisms of cellulose hydrogel will be investigated. For this aim, computational simulation will be used. On an atomistic scale, cellulose hydrogel has different hydrogen bond properties. The OH groups can only act as hydrogen bond acceptors, but due to the negative charge density, there are still more water molecules assembled around adsorbents. Besides intermolecular hydrogen bonding, it has some hydrophobic properties. It means that some hydrophobic materials can be adsorbed on the surface of cellulose hydrogel at specific conditions. Most force fields for this simulation are empirical and consist of a summation of bonded forces associated with chemical bonds, bond angles, and bond dihedrals and nonbonded forces associated with van der Waals forces and electrostatic charge. Empirical potentials represent quantum mechanical effects in a limited way through ad hoc functional approximations.

Keywords

Cellulose · Hydrogel · Adsorption · Computational simulation

1 Introduction

1.1 Computer Simulations of Cellulose

In the past, coordinates from electron diffraction were widely used as starting configurations for computer simulations of cellulose derivative. But one always has to bear in mind the problems connected with the interpretation of raw data. For example, it is very difficult to determine the chain alignment in cellulose crystals [1]. Meanwhile, in the case of native cellulose derivative, the parallel orientation is established, but this question is left unsolved for regenerated cellulose. Cellulose derivative If consists of parallel sheets of hydrogen-bonded chains. This was confirmed by several simulation studies [2].

Previous simulation of various systems, including glucose, cellobiose, and carbohydrates, has been undertaken. Some authors simulated crystal-like cellulose, but under unrealistic conditions, like mini-crystals with only monosaccharide residues and with vacuum boundary conditions. Aablo and French calculated the energies for various packings of cellotetraose molecules [3]. Intra-chain hydrogen bonding occurs between different intrasheet bonding in adjacent planes (a prime indicating a second glucose ring). The conformational space of cellobiose and higher oligomers under vacuum conditions with respect to glucosidic torsions was explored by Hardy using molecular mechanics, both for charged and uncharged models. In the uncharged case, the minima are in agreement with

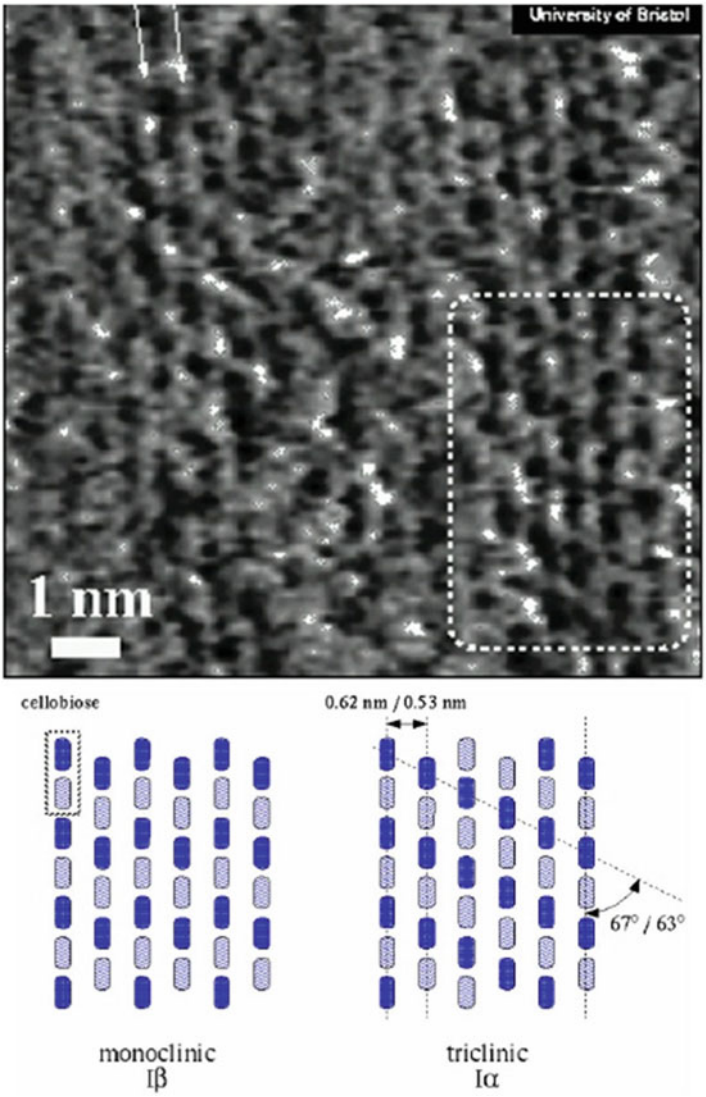

Fig. 1 A software zoom of an AFM image of microcrystalline valonia surface. The arrows point along the cellulose chain direction; the dotted box highlights an area with spots in the length of the cellobiose repeating interval. Bottom: The schematic diagram below shows the expected AFM pattern for monoclinic and triclinic surfaces of cellulose I. Each rectangle represents a single glucose unit [3]

experimental crystal structures of cellobiose and cellulose. However, in the charged model, the appearance of hydrogen bonding distorts this conformation, thereby leading to a new structure [3] (Fig. 1).

1.2 Crystalline Systems and Surfaces

All simulations known from literature deal with the non-orthorhombic unit cells by using monoclinic/triclinic periodic boxes, as implemented in molecular dynamics simulation packages like AMBER or GROMOS. Prework used the cellulose I crystal structure of Blackwell and Gardner, which is now considered to be wrong [4]. Other simulations suffer from a restriction to small systems or from the chosen force field, which does not allow full atomistic details. Recently Heiner performed united-atom simulations of If and If cellulose with the GROMOS force field starting from X-ray diffraction data of Sugiyama. The monoclinic system was built from an ff array of unit cells, the triclinic system from an ff array. Both runs extend over 1000 ns of simulation time. The experimentally observed energy difference between them was confirmed. Most surprising is the small tilt angle observed between glucose ring planes in crystal planes of the monoclinic phase. Alternating chains were termed even and odd; the different tilt angle with respect to the surface was attributed to better interplane hydrogen bonding. More details about the hydrogen bonding pattern were determined using radial distribution functions and energy calculations [2]. The only existing simulation of an cellulose surface was performed by Heiner. In the first paper, the crystal face and, in the second paper, both of them and surfaces were exposed to water. Only the topmost cellulose layers are structurally affected by hydration. The cellulose properties of the interface layers (which are in contact with the solvent) differ only slightly from that of the crystal's bulk. The odd/even duplicity is absent in the interface layers toward water for If and If cellulose, and there are changes in the hydrogen bond patterns, due to completion of cellulose-cellulose bonds with cellulose-water hydrogen bonds. The cellulose-water interface for both the monoclinic and triclinic crystals was classic [5]. From a comparison of the surface-water pair distributions, the monoclinic and the triclinic surfaces are found to be more hydrophobic than the monoclinic and triclinic surfaces. This becomes evident from the first hydration peak, which is repelled from the surface and more unpronounced. In their second paper, the authors focus on similarities and differences between different cellulose surfaces. They found the monoclinic and triclinic surfaces to be very similar. Likewise, the monoclinic surface is similar to the triclinic surface [6]. The latter surfaces are denser and more hydrophilic than the former two. As for f, the odd/even differences disappear on the cellulose-water interface [1] (Fig. 2).

1.3 Carboxymethyl Cellulose

Cellulose is further substituted to cellulose esters and ethers, by either reaction with acid anhydrides or halogen-carboxylate, respectively. An example for cellulose ether is carboxymethyl cellulose (CMC), which is gained by basic conversion of cellulose slurry with sodium chloroacetate or chloroacetic acid [7]. CMC is mass-produced, because of its versatile properties. It is used as thickener, former, or protective colloid. Consumer care products take advantage of its nontoxicity, and it is employed particular for foodstuff and as soil redeposition inhibitor [8]. CMC has a high affinity

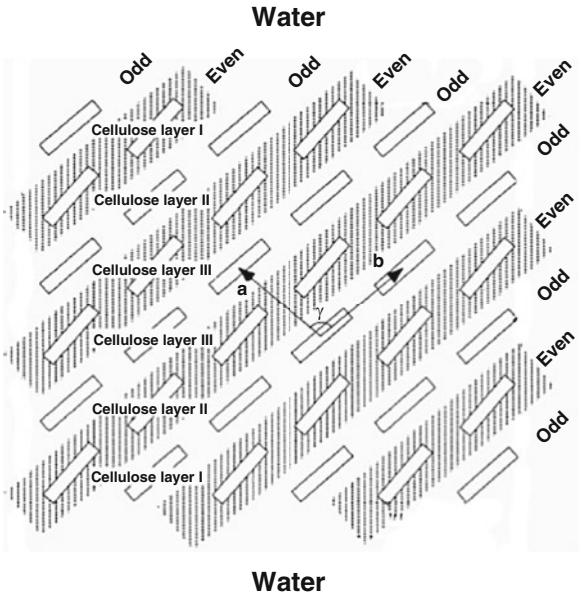

Fig. 2 Schematic picture of the simulation cell of Heiner, taken from. The sketch shows a monoclinic cellulose crystal, the 110 surfaces (top and bottom) exposed to water. Alternate even and odd 200 crystal planes are shaded white and gray. Glucose rings of even 200 planes are tilted with respect to the 200 planes and glucose rings of even planes [1]

to cellulose, and it is therefore a good coating for textiles. CMC coatings improve paper properties, like ink and surface gloss. Crude commercial-grade CMC is produced for detergents, for oil-drilling, or for the paper industry. Product properties of CMC are mostly determined by the degree of substitution (DS) and the substituent distribution within one anhydroglucose unit (AGU) and along the CMC chain. The degree of substitution ranges from zero (no substitution) to three (all three hydroxy groups of a glucose unit substituted). In the case of heterogeneous cellulose derivatization, statistical substitution patterns and polydisperse CMC are produced. The chemical characterization of CMC is almost restricted to the average degree of substitution, which is measured by titrimetric methods or chromatography where the persistence length of CMC is found by size exclusion chromatography to be 20 nm [9]. Owing to this, only little information is available on the interplay between the CMC structure (substitution pattern, degree of substitution) and its macroscopic properties. The actual substitution pattern of industrial cellulose derivatives can be rationalized by both kinetic and energetic arguments if cellulose is produced as alkaline slurry. Hydroxyl groups can only be carboxy-methylated if the bulk cellulose is swollen and hydroxyl sites are free from hydrogen bonding and accessible to the solvent and substituting agent. The carboxy methylation reaction takes place at the solvent-cellulose phase boundary [10]. From this, the dynamics of swelling and hydrogen bond cleavage are responsible for the degree of substitution and the

substitution pattern. The glucosidic linkage of CMC was hydrolytically cleaved, and on this way, information on the distribution along the backbone was lost. The same results can be found by high-pressure liquid chromatography, which allows separating and identifying differently substituted units. There are eight different substituted monomer units possible. CMC polyelectrolyte properties are only understood from a technical point of view. There is a good experience how to tailor a CMC through the production procedure to a certain property, like a high viscosity. The underlying molecular chemistry is still beyond our knowledge. The missing link between microscopic structure and macroscopic properties can be established by molecular dynamics simulations [11].

1.4 Nanocellulose

The various forms of nanomaterials that can be produced from cellulose are often collectively referred to as cellulosic nanomaterials or nanocellulose [12]. For example, the extraction of cellulose nanofibrils (CNFs) and cellulose nanocrystals (CNCs) from plants, bacteria, and some animals (e.g., tunicates) is leading to a wide array of worldwide research to use these nanomaterials in product applications [13, 14]. Examples include using CNFs as reinforcing agents in composites due to their high strength properties, relative low cost, and availability or CNCs due to their incredibly high strength (Fig. 3), renewability, lightweight, high surface area, and unique photonic characteristics [15]. As you will see when reading this book, research and development is currently taking place worldwide within academia, industry, and government agencies to study, characterize,

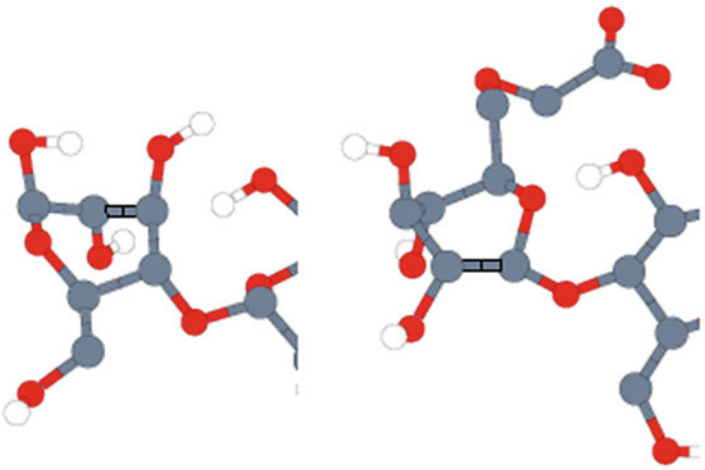

Fig. 3 Two terminal anhydroglucose units during the initial phase of a CMC I equilibration. The 4C1 conformation is lost and the OH oxygens take an axial position. Both rings are twisted neither in a proper chair nor boat form

and use these highly complex cellulosic nanomaterials. Nanocellulose in its various forms contains unique structures and self-assembly features that we can exploit to develop new nano-enabled green products. A specific example is the use of cellulosic nanomaterials in lightweight, high-performance composites. Such nanocellulose-enabled composites could eventually replace carbon fiber mats and strands by weaving cellulose-derived nanomaterials and fiber into mats. This could lead to replacement of the nonrenewable and fossil-based materials currently used to make automotive parts such as dashboards, seats, floor mats, and even body panels or frames. The world may not be ready yet to step back into a wooden airplane, but the day will come when aircraft will have wings and fuselage components containing lightweight, high-performance nanocellulose-enabled composites. Fiberglass is a common composite with which most people have experienced. It is used to manufacture diverse products including tool handles, sporting goods, bike frames, boats, and even the bodies of some sports cars. Fiberglass cannot be made transparent and is a heavy material for a composite. Replacing fiberglass mat with nanocellulose-containing mat could lead to new lighter-weight materials and the eventual replacement of nonrenewable products with sustainable and renewable cellulosic materials [14].

1.5 Polyelectrolytes

Polyelectrolytes play an important role in industrial chemistry. The fields of application range from tailor-made thickeners to paper finishing or ore preparation. Polysaccharide derivatives represent one interesting class of polyelectrolyte. In particular, cellulose products are important compounds [16]. For our simulation study, carboxymethyl cellulose (CMC) is chosen as an example for a polyelectrolyte derived from a natural polymer [17]. Aqueous CMC solutions exhibit valuable properties, like a wide range of viscosity, nontoxicity, and biodegradability. Particularly for the high-purity consumer-product market (cosmetics, food stuffs), CMC is used. However, pricing becomes more important in bulk applications (clay and ore treatment, oil-drilling). Hence, it is desirable to replace some of the high-cost high-selective chemicals with low-cost equivalents, like polypeptide, which is the prototype of medical synthetic polyelectrolytes. Polypeptide is the other polymer studied in this work. Most published works on aqueous CMC and polypeptide solutions were done experimentally using chromatography, C nuclear magnetic resonance, and rheological techniques [18]. Theoretical approaches are scarce. We are aware of only one paper, which treats CMC by the wormlike chain theory. This electrostatic theory successfully rationalizes some of the global properties of CMC, but as a rather generic approach, it does not allow for detailed predictions on an atomistic time and length scale. Similar restrictions apply also to Monte Carlo simulations of polyelectrolyte chains in a cell model, where the solvent is treated as a dielectric continuum. Especially local interactions such as hydrogen bonds (hydrogen bridges) are neglected in theories and non-atomistic simulations. With two or

three hydrogen bond donor groups per repeat unit and even more acceptor sites (including charged COOH groups), this type of interaction is likely to be very important for the behavior of CMC in water. Experimental techniques, on the other hand, suffer from different problems: NMR provides averaged local properties. Rheology derives and verifies scaling laws, but different polyelectrolytes lose their chemical identity and show the generic behavior of excluded volume chains. Atomistic molecular dynamics (MD) simulations cannot overcome all these problems, but they can provide some more detailed information [19].

Polypeptide is important for industrial applications because of good water solubility and as a (strong) model polyelectrolyte in science. Polypeptide is known for only weak adsorption to cellulose but binds with hydrophilic glass (SiO_2) surfaces. At high concentration, polypeptide forms networks, cross-linked by hydrogen bonds and entanglements. The water structure around the polyelectrolyte was investigated by Tsukida et al. using Raman spectroscopy. They found a high perturbation of water-water hydrogen bonds at a degree of neutralization below 10 and concluded that a certain amount of carboxylic groups enhances water-hydrogen bonds in the polymer vicinity. There is a minimal disruption of hydrogen bonds near a degree of neutralization. Even at higher ionization, polypeptide is assumed not to be fully stretched. The local conformation of polypeptide is assumed not to be dependent on ionization or salt concentration. Like in the case of CMC, no experimental method has been applied, which goes beyond a macroscopic view of PP. Methods applied to polypeptide are rheology, viscometry, light scattering, and calorimetric methods. The only simulation work was done by Ullner et al. This is a Monte Carlo study of one polypeptide chain in solution. But even though counterions are accounted for explicitly, the simulation is done in the generic cell model for polyelectrolytes [20]. However, there is some agreement that polypeptide behaves like a flexible coil in a “good solvent” instead of having rodlike structure. One aim of this thesis is to understand better the structural and dynamic aspects of the hydration of CMC and polypeptide and to compare the two polymers. To this end, we investigate both the chain properties and the interaction of chains with their immediate solvent environment. Atomistic simulation is confined to the study of small system sizes. However, in combination with coarse-graining methods, even some mesoscopic properties may be explored. Thus, a second goal of this study was to produce atomistic structural information, from which coarse-grained models of, e.g., polypeptide and the cellulose surface can be generated. The coarse-grained models can be used to study the adsorption of polyelectrolytes on cellulose beyond the size and time limitations of atomistic molecular dynamics [21].

2 Materials and Methods

Computer simulations came into fashion among scientists, as fast hardware became affordable. Early computer simulations were done on the MANIAC computer in Los Alamos by Metropolis and Rosenbluth. From this milestone in scientific computing, character and size of simulated systems changed. In the first

years, there was research to develop, validate, and try new methods, even with simple systems like hard spheres, where often a theoretical solution was already present. With the Lennard-Jones potential, it was possible to compare the outcome of simulations with experimental results. There was a need for a new method to simulate not only static properties (ensemble averages) but extend simulation to explore dynamical (transport) properties as well. Molecular dynamics (MD) is the new technique. If a given system follows Newton's equation of motion and we know one state of the system, then we can calculate every state of the system (both in the future and in the past). Classical particles are moved by integration of the system's equation of motion in time. By means of this, a molecular dynamics simulation is very simple; after initialization, the simulation cycles through successive molecular dynamics steps. For each step, the force is calculated, particle velocities plus positions are updated, and finally, properties of interest are sampled.

This was first done for hard spheres by Alder and Wrainwright and later by Rahman for Lennard-Jones particles. Later, the method was extended to molecular systems (by the introduction of bonds) and different algorithms devoted to handle different ensembles and conditions like nonequilibrium molecular dynamics. In particular, the Lennard-Jones potential has proven useful, and it is the most common model for nonbonded interactions.

The work of Rahman was pioneering, because it showed the benefits of molecular dynamics simulation over theoretical approaches, which often fail to describe. Moreover, MD is valuable also for nonideal, multiparticle systems. One recent example to show the versatility of the method is the dissipative particle dynamics method. Even if it is still based on the simple molecular dynamics scheme, it can be used for mesoscopic simulations through a modified equation of motion. The second route to handle large systems is to use more elaborated programs on multiprocessor computers. This enlarges the number of simulated particle from about on a workstation to several million particles on a supercomputer. To mention but a few trends in atomistic molecular dynamics, these are the calculation of free energy-related properties; the application to larger molecular systems, like polymers or biopolymers; the programming of user-friendly simulation programs to allow for easy standard calculations; and the development of new and better force fields. The last item development of force fields is very crucial. Although there exist a variety of different force fields, none of them describes all faces of a system completely. In consequence, there are many force fields available, and it is not always clear in advance, which one will give the best results to our questions. In other words, there is nothing like unique natural force fields for a given molecular or system: Even approaches with a high number of terms do not necessarily give good results [22]. The general layout is almost the same for all common force fields. They divide interactions into nonbonded (Lennard-Jones dispersion repulsion interaction, Coulomb electrostatic interaction) and bonded (bonds, angles, torsions, etc.) [23]. Some force fields employ special terms to treat hydrogen bonds or similar phenomena, but this is not very common, as a good description may be obtained by other terms as well.

2.1 Force Fields

While the kinetic part of the Hamiltonian uses only particle masses as parameters, the potential energy part is dealt with by a force field. The force field is the major choice or input of a simulation. It gives an expression for the potential energy as a function of particle coordinates (r). This expression consists out of different terms, which are usually chosen intuitively to mimic the nature of molecules. The splitting of the potential energy into a sum of bonds, angle, and other terms is arbitrary and only rejects a human understanding of chemistry. The second approach to a force field is the pragmatic, technical one, where terms are not even meant to have a special physical meaning but originate from some technical issue or procedure. To name but a few technical force field contributions, there are position restraint terms to keep atomic sites fixed in space or bond constraints to keep the distance between atoms constant. Nevertheless, the use of force fields instead of true electronic interactions has proven useful in lots of simulations from simple Lennard-Jones systems to much more complex molecular systems.

2.2 Nonbonded Interaction

The separation of a force field into distinct mathematical terms in molecular simulation is justified usually by computational convenience or reasons of transferability. There is no question that all interaction would have to be calculated by quantum mechanical methods. Unfortunately, this way is by far too time-consuming, even if fast semiempirical methods are employed. For systems with more than several thousand or even hundreds of thousands of atoms, it is inevitable to use a force field with pairwise additive terms. All electronic degrees of freedom are ignored, and every atom is taken as the position of its nucleus. Methods which rely on this statement are commonly summarized under the term molecular mechanics. Energy functions are called "effective potentials," as they try to incorporate many-body effects into a site-site potential. They do not resemble the potential as it would be correct for two interaction sites in vacuum but are representative for say two argon atoms in liquid argon. On one hand, this is an important breakthrough, as we do not bother about the explicit calculation of many-body terms, but on the other hand, this may reduce transferability of a parameter set, as there is an influence of the environment onto a single site's force field parameters. This leads to a rough categorization into force fields for inorganic (crystal) and for organic (soft) matter and for solutions, the latter one with a special emphasis on water as solvent. Some force fields are very biased toward aqueous solutions of (bio) organic compounds like DNA or carbohydrates. To achieve transferability, which is often considered a key property of force fields, the energy function is divided into several contributions. To name but a few, there is a bond term, often modeled by a spring, or a bond angle modeled by a harmonic angle

potential. Nonbonded interactions are divided into electrostatic and dispersion/repulsion (induced dipole, Pauli repulsion) contributions:

One example is the dispersion energy, which is often expressed as a (computationally cheap) Lennard-Jones potential, but some approaches use the Buckingham form, which models Pauli repulsion using an exponential function. Knowing the potential between two sites is only the first steps toward calculating the energy of a N-body system and all forces. Instead of using an order N double loop over all site-site combinations ij, the most efficient way is the use of a cut of rc together with a neighbor list to speed up the simulation by a factor of order N. This is a point where physical and technical issues meet and compete. From a physical point of view, one wants to take the cutoff as large as possible, but with limited computer resources, one should take it as short as possible.

2.3 Bonding Interaction

Bonding interactions are somehow better to understand, because their concept is rather intuitive. Usually they define some minimum energy state in terms of an equilibrium angle or bond distance. Deviations from this value impose an energetic penalty. The only exception are bond lengths, which if treated by a harmonic spring would require very tiny time steps and are thus not feasible. The bond vibrations of large molecules are of no interest. Therefore the harmonic bond potential is replaced with a rigid constrained bond, which on the one hand introduces additional calculations into the molecular dynamics simulation but on the other hand allows increasing the integrator's time step ft by one order of magnitude.

2.4 Constraint Dynamics

The SHAKE procedure of Ryckaert, Ciccotti, and Berendsen is one of the most explained and cited paper in molecular dynamics. The SHAKE method allows us to consider atomic connectivity without using harmonic bonds. Valence bonds vibrate at high frequency and impose a small integration time step to a simulation. SHAKE now alleviates this shortcoming by fixing (constraining) the distance r between two sites to a parameter value. This equality is usually written down in the form of a holonomic constraint.

First the unconstrained motion of all atoms is calculated and after the equation of motion is expanded by the introduction of a constraining force (as a Lagrange multiplier). The resulting equations of motions are now solved in an iterative fashion until all constraints k in the equation are within some tolerance. Our simulation packages use a special SHAKE algorithm, which performs well on vector machines like the Cray T or NEC SX.

2.5 Other Force Field Terms

Besides the nonbonded Lennard-Jones and Coulomb interaction and the constrained bonds, there are several other force field terms. They are computationally cheap and more generic as, for example, the nonbonded potential parameters. Examples include bond angles and bond torsions.

2.6 Periodic Boundary Conditions

Periodic boundary conditions are the way to generate pseudo-infinite systems, thus simulations which do not suffer from boundary or edge effects. Periodic boundaries are achieved by putting a grid of copies around the central simulation box. The algorithm ensures that no interatomic distance in one direction is larger than one box length (this holds strictly only for orthorhombic boxes). To calculate the force on a site in the central box, neighbors from the central and surrounding boxes are used, if they are within the cutoff distance. If one atom travels out of the central box, it reenters at the opposite side of the box. The internal coordinate format does not store these folded but unfolded coordinates, so that the folding is applied in the force loop. To avoid self-interaction, the box has to be larger than two times the cutoff.

3 Results and Discussion

3.1 Interactions and Force Fields

The actual parameterization of the GROMOS force field for carbohydrates has evolved since 2000 and was mainly tested on cyclodextrin, as well as on other sugars. Kroon-Batenburg, Bouma, and Kroon made use of the GROMOS parameter set for simulations of cellulose in solution and compiled an overview of different parameter sets in conjuncture with Ewald sums by Kouwijzer et al. One application of the GROMOS force field to crystalline cellulose was reported by Heiner, Teleman, and coworkers. Their simulations covered both the crystalline phase of cellulose and the interface with water. The successful simulations and the compatibility of the GROMOS force field terms in particular the treatment of electrostatics without an Ewald sum were decisive factors to choose the GROMOS force field. A second point is our interest in multicomponent, heterogeneous systems, with both a cellulose surface, a solvent, and a polyelectrolyte solute molecule. Our force field of choice should be able to give a good description for every component, not only of the sugar. So the use of a building block based and thus force field is sensible. However, there are plenty alternatives for carbohydrate force fields. Besides generic ones, like AMBER, CHARMM, and the OPLS, parameter sets, some authors developed special approaches for carbohydrates. Most of these expert models

have some special application in mind, like the exploration of anomeric equilibrium of sugar rings. An overview is given by French and in various articles published in a special issue Carbohydrate Modeling of the *Journal of Molecular Structure*. A recent approach was done by Neyertz et al. to develop a cellulose all-atom potential model from various origins (mainly from other sugar parameters and quantum chemistry). Despite the mixed sources, the Neyertz approach reproduces unit cell parameters, thermodynamic stability, and moduli in close agreement with experiment. Tests or applications for this force field in solution are not known yet. The authors develop the force field with PEO-cellulose interface simulations in mind. In contrast to the Neyertz model, the GROMOS approach is a so-called united-atom force field. Aliphatic oxygens are not modeled by an explicit interaction site. Only polar/OH hydrogens are explicitly treated. Aliphatic hydrogen atoms are accounted for by a change of the parameters for the parent carbons, which grow in size (+%) compared to all-atom force field (like AMBER) and get a higher minimal energy (+%). For organic materials, this has proven feasible if the stereochemistry at chiral centers is preserved using additional terms in the parameterization. The GROMOS force field tackles this by harmonic dihedral angles, which fixes four atoms in a given tetrahedral geometry. The major benefit is the reduced amount of computer time. However, for our cellulose-water systems, the savings are less pronounced. Even if the united-atom model removes one third of all atoms for a glucose ring (aliphatic hydrogens), there is still the large amount of polar hydrogen sites left.

Torsions in the GROMOS force field are considered by (a) the torsion potential and (b) modified interactions. United atoms separated by exactly three bonds interact through a reduced Lennard-Jones potential. For atoms other than united atoms, the interaction is not modified. The sum of both terms results in a physical torsional potential. There is usually only one torsional term for each bond i-j-k-l, but this rule is changed for sugar rings, where additional torsions guarantee for the correct ring puckering. All interactions are dealt with by some force field term (bonds, angles); all atom pairs with a topological distance greater than four bonds interact by unmodified nonbonded interactions. We make use of an effective model potential. This is because the parameter set is chosen to incorporate many-body effects by the physicochemical environment. For example, charges are taken to reproduce average polarization effects by the solvent. Because of this, we avoid mixing of different force fields and used SPC-water (simple point charge) throughout, where parameters harmonize well with the GROMOS cellulose force field. Furthermore, it is a rigid model, and it has the minimal number of sites, which makes it computationally efficient. The CMC and polypeptide force field terms were taken to be compatible with the cellulose parameters. Because of this, CMC and polypeptide are modeled with the GROMOS force field as well. The CMC parameterization is based on cellulose, with extra parameters for the CH–COOH group. The CH parameters were taken from an aliphatic sub-chain in the GROMOS force field, and the carboxylic group is an generic parameter set which is used for all kinds of carboxylic acids in the GROMOS handbook.

3.2 Computational Details: Polyelectrolyte in Dilute Solution

For the polyelectrolyte simulations in dilute solution (CMC and polypeptide with counterions but without a surface), a single oligomer was solvated in about (see below for exact numbers) water molecules. The water configuration has been prepared from a cubic centered lattice by an equilibration run of 1000 ps until density converged. The initial polyelectrolytes' configurations were generated from a Z-matrix for a linear molecule. The sodium counterions were placed into the simulation box at random but not closer than 5 nm to any atoms of the solute. All coordinate sets were joined together, and overlap was removed by either f removing water molecules, closer than 9 nm to any of the solute atoms, or f pushing overlapping water molecules away from the solute: All water molecules in the vicinity of the solute are moved away from the polyelectrolyte along a solute water vector r, defend for every water molecule. The displacement vector starts at the polyelectrolyte site, which is closest to the water oxygen and ends at this oxygen. The length of the vector is scaled by an exponential decay function (jrj = c); c was chosen by trial and error to be nm. Water molecules far apart from the solute are hardly displaced at all (Figs. 4 and 5).

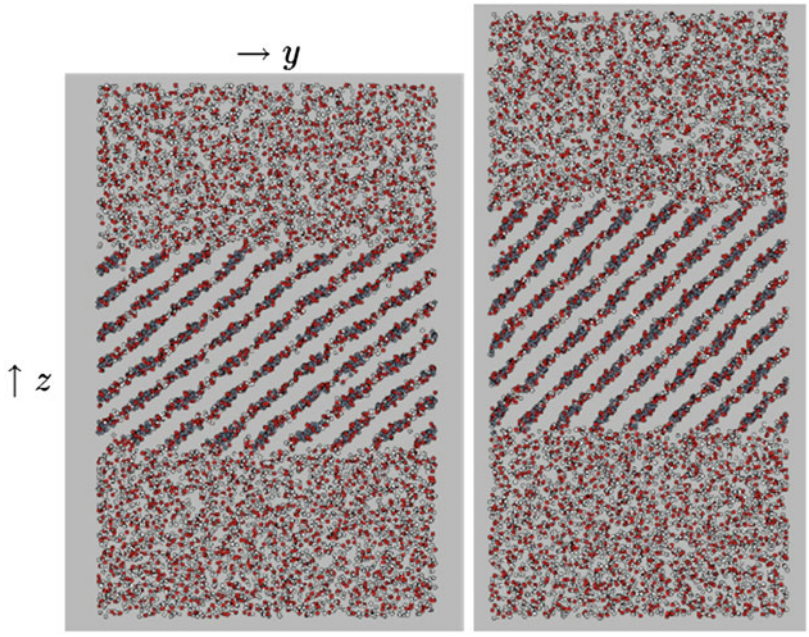

Fig. 4 Pictures of surface-water simulations after equilibration of about 400 ps. Left: 110-cellulose (wide), Right: 1–10-cellulose (narrow). The cellulose chains run into the drawing plane (x-direction)

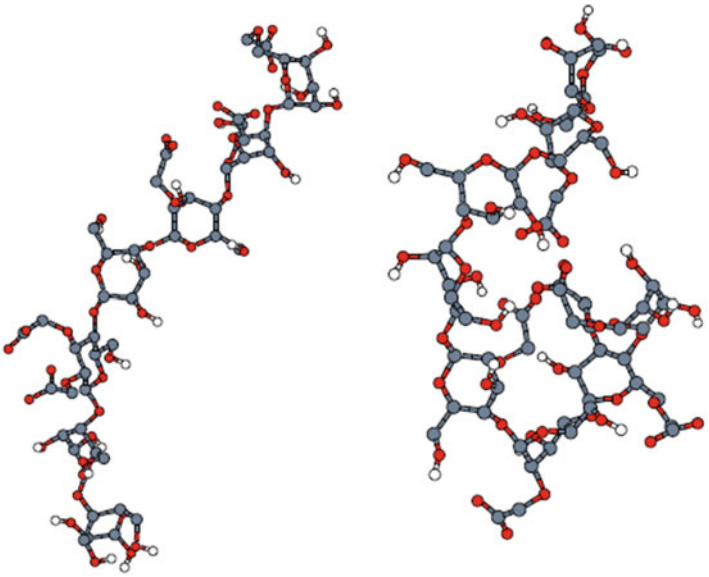

Fig. 5 Snapshots of CMC I (left at 2:0 ns simulation time) and CMC IIa (right at 3 ns)

3.3 Computational Details: Cellulose Surfaces

We examined two different cellulose-water systems: The first one with an interface between the monoclinic surface and water and the second one with the monoclinic surface exposed to water. The simulation setup is almost identical with that used by Heiner. A slab of six cellulose layers has two interfaces toward water. The z-axis of the periodic box is parallel to the normal of the respective surface. The cellulose crystal's c-axis (chain direction) runs along the Cartesian x-axis. Eight cellulose chains of each three cellobiose units are staggered with a shift of c = along the periodic box's y-axis. However, the simulation of the monoclinic cellulose surface employing an orthorhombic simulation box leads to some distortions of the molecular coordinates. The deviations from the native monoclinic structure are minor and were neglected. The exact procedure, to change the unit cell's geometry, is described. In the angle, from a small change of the monoclinic cell, we arrive at a unit cell which packs into an orthorhombic lattice.

3.4 Computational Details: Aqueous Polyelectrolyte-Cellulose Systems

The third kind of systems examined was the combination of the two systems above: A cellulose-water interface simulation with CMC or polypeptide oligomers dissolved in the aqueous phase. As the oligomers of CMC and polypeptide described

above are too large to fit into a reasonable sized cellulose-water simulation box, we used smaller oligomers: For CMC the first molecules, CMC I was cut into two pieces, a trimer and a tetramer with molecular weights.

With two polymers and two different surfaces, we have four possible solute-surface combinations. The polymers are irregularly placed into the dense water system, by shifting water molecules away from the solute atoms radically as described on page 14. By this procedure, we obtain suitable starting coordinates without overlapping atoms. The cellulose sites are fixed in space using position restraints, and the system is quenched into a low energy stat, and equilibration is started afterward without position restraints. All simulation parameters (temperature, time step, weak coupling, etc.) are as for the cellulose-water system. Cellulose and water coordinates are taken from the respective cellulose-water simulations. an overview over all four solute-surface simulations.

The carboxymethyl side groups are strong H acceptors, because of their flexibility from the carbohydrate backbone and because of their negative charge. The globular CMC conformation is both stable through a multinanosecond simulation and builds dynamically from a stretched starting geometry. On a local scale, the globular conformation undergoes less hydrogen bonding with the solvent, as more intramolecular H-bonds are present and some H-donor and acceptor sites are buried inside the globule and are not accessible to water. This is also visible in the CMC-water radial distribution functions, where the globule state has a more distorted and irregular hydration shell. The polypeptide oligomer in aqueous solution is stretched and is readily solvated by water molecules. Because polypeptide has a high charge density on COOH groups, the mass of salvation water exceeds the polymer's own mass by a factor. The hydrogen bonding for CMC is more complex. There is inter- and intramolecular hydrogen bonding, latter one can be subdivided into inter- and intraglucose-ring bonding. For the collapsed, globule CMC molecules, all kinds of H-bonds are found in a significantly amount. Most remarkable are H-bonds spanning six or seven glucose rings, thus closing the CMC chain to a ring [24].

There are only few counterions close to the CMC strand (about Na^+-ions/AGU). The PP sodium radial distribution function is better defended due to the higher number of counterions. There are about sodium ions under the first peak of the PP-Na^+-rdf. The difference between CMC and polypeptide is understood, as the main interaction of sodium takes place with the carboxylic side groups of the polymers, which favors PP [23]. Counterions play a role during the (dynamic) collapse of the second CMC molecule. Simultaneous with the collapse, the number of sodium ions close to the backbone raises. The increased concentration of positive charges screens the repulsion of COOH groups and initiates the collapse. Two crystal planes of the monoclinic cellulose crystal were simulated for several nanoseconds with an interface to water. Both surfaces are representative for other surfaces like the triclinic ones. The surface has a wider interchain spacing than the surface. Both surfaces are stable against water and they are not penetrated by the solvent. This is due to the mainly hydrophobic and lipophilic character of both surfaces. This property has been accessed either through water densities on the surface [25].

4 Conclusion

Even though poly(acrylate) and (carboxymethyl) cellulose both are water-soluble polyelectrolytes, their behavior in water and toward water differs markedly. This is due to the different charge densities as well as to the different types and qualities of hydrogen bonds that either form with water. In PP, there is one strong hydrogen bond with the deprotonated carboxylate acting as an acceptor. In CMC, the smaller density of carboxylates is only partly offset by the possibility of alcoholic OH groups participating both as donors and as acceptors in hydrogen bonds. Hydrogen bonds to the ether oxygens are irrelevant. Taken per molecular weight of the polymer, it seems safe to say that polypeptide forms at least twice as many hydrogen bonds to water as CMC and that they are of larger binding energy (charge-dipole, rather than dipole-dipole). Based on this argument, the salvation of polypeptide in water should be more exothermic than that of CMC. Unfortunately, no measurements appear to be available for comparison. The comparison of the two CMC oligomers shows that the particular carboxymethylation pattern has an immense influence on the local structure in solution. The two assume entirely different conformations: CMC I is stretched and flexible, whereas CMC II favors a rigid cyclic conformation. We are therefore left to conclude that industrial CMC with its statistical substitution of OH groups behaves locally very diversely. As a consequence of its globular structure, CMC II shows more intramolecular hydrogen bonds than CMC I, fewer hydrogen bonds to water, slower hydrogen bond dynamics, and more contacts with the counterions. Aqueous polyelectrolyte solutions of carboxymethyl cellulose (CMC) and poly(acrylate) (PP) have been investigated. With respect to the size and CH-COOH distribution pattern, two aqueous solutions of different CMC oligomers (one heptamer and octamer) result in two chain structures: We observe one stretched structure, which is for a polyanion is rationalized by repulsion of negative charges, and a globule-like, collapsed structure. The compact structure is held together by intramolecular hydrogen bonds, which bridge multiple anhydroglucose units and often involve COOH groups.

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Multifunctional Hydrogels

13

Min Xu and Hailong Huang

Contents

Abstract

Hydrogels are cross-linked three-dimensional polymeric networks which can absorb a great quantity of water and keep mechanically stable without dissolution. Due to the biocompatibility and biodegradability, biological hydrogels have been

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wildly investigated and used in various fields, such as adsorption materials, shape memory materials, self-healing materials, sensor units, super capacitor, drug carriers, and so on. In this chapter, we would focus on some of the upper aspects and give a brief introduction.

Keywords
Hydrogels · Adsorption · Stimuli-responsive · Self-healing

1 Introduction

Hydrogels are three-dimensional hydrophilic polymeric networks and are typically soft and elastic, owing to their compatibility with water. Cross-links and interconnections, which make polymer chains get together, can be formed by physical entanglements or chemical bonds, leading to physical and chemical hydrogels. Chemical hydrogels can be formed by chemical reactions such as radical polymerization [1], photopolymerization [2], high-energy radiation [3], and covalent conjugation [4]. These hydrogels generally show good physical stability and mechanical strength. Physical hydrogels are composed of polymer self-aggregation via non-covalent interactions such as hydrogen bonds [5], hydrophobic interactions [6], electrostatic interactions [7], inclusion complex [8], π–π stack [9], ionic interactions [10], crystallinity [11], and other affinity interactions [12]. These hydrogels exhibit excellent swelling and absorption capacities. Based on the raw materials and synthetic methods, the hydrogels can be classified to be petroleum-based hydrogels or bio-based hydrogels, covalent or physical hydrogels, copolymer networks or interpenetrating networks, degradable or nondegradable hydrogels, and so on. Due to their unique characteristics, hydrogels have been extensively studied in bioscience and material science and widely applied as functional materials, for example, contact lenses [13], disposable diapers [14], wastewater treatments [15], and moist pads for healing wounds [16] or burns [17]. In this chapter, we would like to introduce the advanced research and applications as follows: (1) adsorption hydrogels, (2) stimuli-responsive hydrogels, and (3) self-healing hydrogels.

2 Adsorption Hydrogels

Attributed to the network structure, hydrogels have excellent adsorption capacity to absorb large quantity of water and keep stability. Through designing functional molecular or modifying natural products, the hydrogels can provide complexing sites for the templates as adsorption materials. Recently, lots of researches are dealing with the use of hydrogels for adsorption materials, and also many researchers are investigating the hydrogels for wastewater treatments.

2.1 Wastewater Treatments

With the development of industry, environmental pollution has received great attention and became the focus of research. Water pollution, especially heavy metal ions and organic dye, is a menace to health. Many methods are used to purify water, such as chemical separation, electrochemical separation, adsorption, and cation exchange. Among these methods, adsorption is the most high-efficient method with high adsorption capacity, selectivity, and reusability. In recent years, many researchers pay attention to natural materials and polymer composites for the removal of pollutants from water, which have received excellent achievements.

2.1.1 Broad Adsorption of Heavy Metal Ions

Biomaterials, such as cellulose, chitosan, and their composites, are fitful to be the matrix to prepare adsorption materials for heavy ions [18–22]. A typical composite is cellulose–polyetherimide (PEI) composite hydrogel [23]. It was prepared in alkali/urea solution system with PEI as functional group and cellulose as skeleton in Fig. 1. The composite hydrogel showed good adsorption capacity of heavy metal ions such as Cu(II) 253.8 mg/g, Ni(II) 112.2 mg/g, Zn(II) 148.4 mg/g, Cr(III) 30.4 mg/g, and Pb(II) 248.2 mg/g as shown in Fig. 2. The thermodynamics and kinetics of the system were also studied. The adsorption process followed pseudo-second-order kinetics equation, and the adsorption capacities of cellulose/PEI composite hydrogel were much higher than activated carbon-based adsorption materials. Hence, cellulose/PEI composites could be potential materials for wastewater treatments and the recycling applications of heavy metal ions.

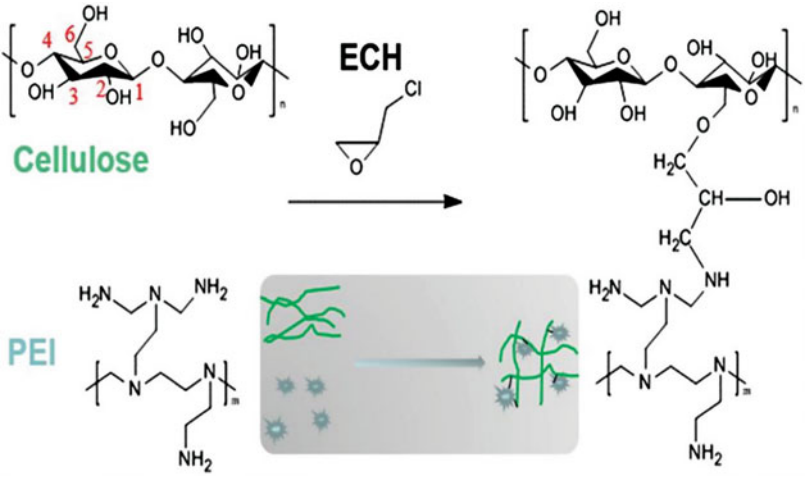

Fig. 1 Proposed mechanism for cross-linking reaction of cellulose and PEI in alkali aqueous solution with epichlorohydrin (ECH)

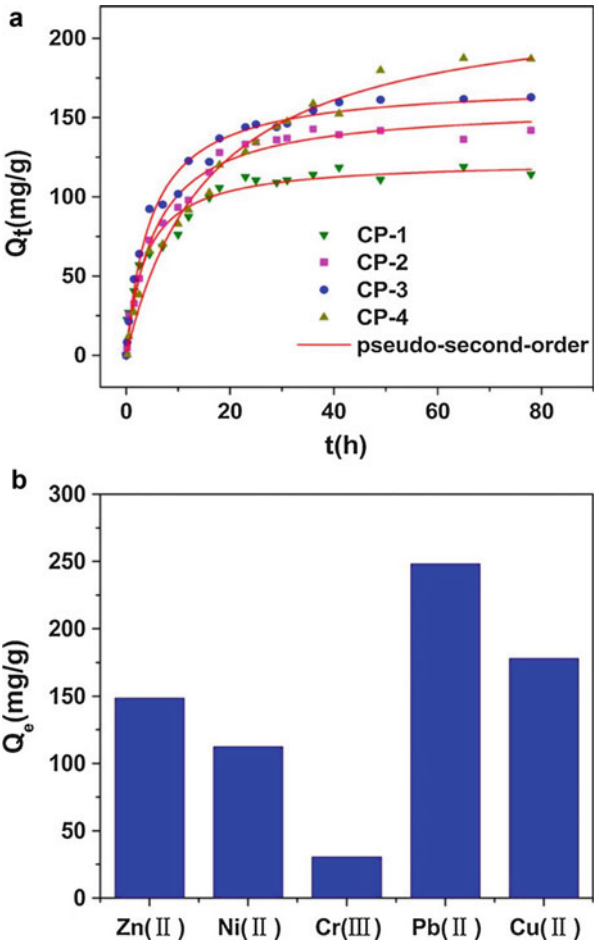

Fig. 2 (**a**) Effect of contact time on adsorption of cellulose/PEI composites. Conditions: initial concentration, 500 mg/L; room temperature. CP-1, cellulose/PEI (4:5, wt%); CP-2, cellulose/PEI (2:5, wt%); CP-3, cellulose/PEI (2:10, wt%); CP-4, cellulose/PEI (2:20, wt%). (**b**) The adsorption capacity of cellulose/PEI composite on Zn(II), Ni(II), Cr(III), Pb(II), and Cu(II). Conditions: cellulose/PEI composite (CP-2); initial concentration, 1000 mg/L; adsorption contact time, 80 h; room temperature

Because of efficient separation, magnetic technology has become an attractive method to solve the recycling problems of adsorption material. In recent studies, carboxylated cellulose nanofibrils(CCNFs)-filled magnetic chitosan hydrogel beads [24] (m-chitosan/poly(vinyl alcohol)/CCNFs) were prepared by an instantaneous gelation method as shown in Fig. 3. The magnetic hydrogel was used as adsorbents for Pb(II) ions (171.0 mg/g). The adsorption isotherm was fitted by the Langmuir model and the adsorption kinetics closed to pseudo-second-order model. Moreover, the hydrogel could be easily separated by magnetic field and regenerates in weak acid solution. It showed good reusable ability after four cycles keeping 90% adsorption capacity. M-chitosan/poly(vinyl alcohol)/CCNFs hydrogel could be considered as a promising adsorbent for the removal of Pb(II) ions for the high adsorption capacity, fine biodegradability, and the ability to be rapidly separated from aqueous solution (Fig. 4).

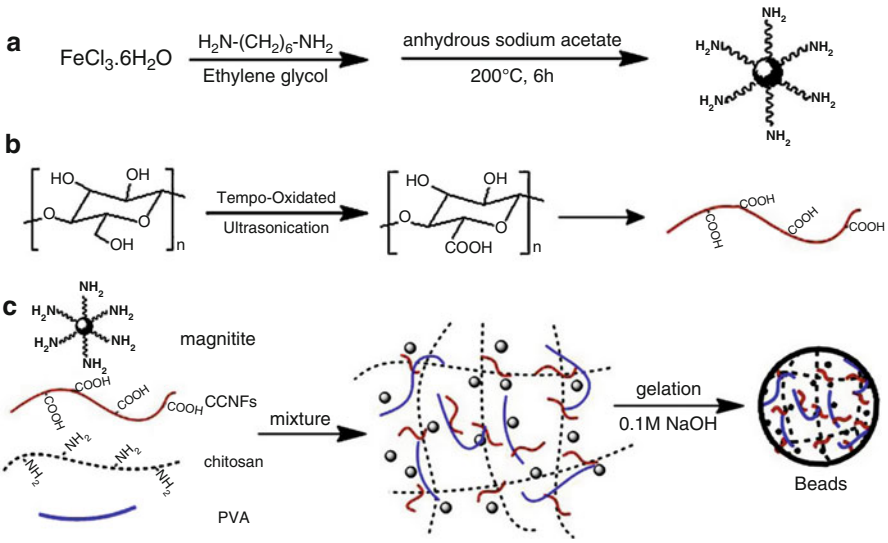

Fig. 3 Proposed mechanistic pathway for the preparation of magnetite nanoparticles (**a**), CCNFs (**b**), and m-CS/PVA/CCNFs hydrogels (**c**)

2.1.2 Selective Adsorption of Metal Ions

Sometimes, we need to recycle some certain metal ions, for example, lithium ion. Due to the large solubility product constant of lithium carbonate, the lithium ion is very difficult to be completely retrieved. Many methods have been developed to retrieve lithium ion, such as biological recovery, precipitation recovery, and adsorption recovery. Among them, adsorption is a cost-effective and environmental friendly method for recovering lithium from aqueous solution. However, most adsorbents are nonspecific, showing low selectivity toward a specific metal. Therefore, a novel magnetic ion-imprinted polymer (IIP) with a core–shell structure (Fe_3O_4@SiO_2@IIP) [25] was synthesized by a surface imprinting technique using 2-(allyloxy)methyl-12-crown-4 as the functional monomer, lithium ion as the template, and ethylene glycol dimethacrylate as the cross-linker (as shown in Fig. 5). Fe_3O_4@SiO_2@IIP showed fast adsorption kinetics for lithium ion (10 min to reach complete equilibrium), and the adsorption process obeyed an external mass transfer model. Homogeneous binding sites were proved by the Langmuir isotherm, and the maximum adsorption capacity was 0.586 mmol/g. Fe_3O_4@SiO_2@IIP showed excellent selectivity for Li(I), and the selectivity separation factors of Li(I) with respect to Na(I), K(I), Cu(II), and Zn(II) were 50.88, 42.38, 22.5, and 22.2, respectively, as shown in Fig. 6. The adsorption capacity of the adsorbent remained above 92% after five cycles. This study offered a good method for Li's recovery.

2.1.3 Adsorption of Organic Dyes

A novel environmental friendly composited hydrogels of hydroxypropyl cellulose (HPC) and molybdenum disulfide (MoS_2) were prepared [26]. The obtained

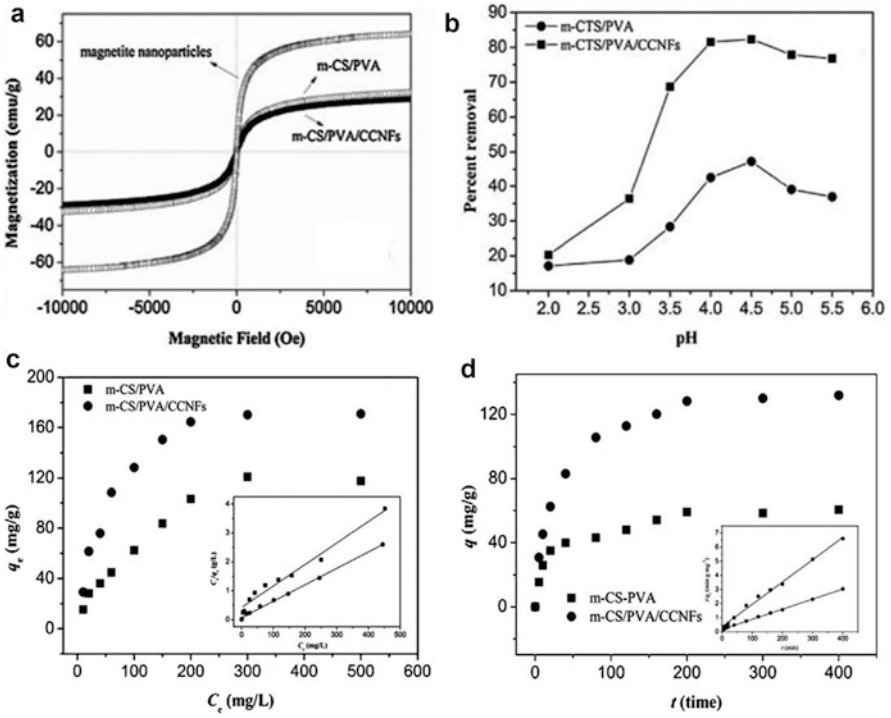

Fig. 4 (**a**) Magnetization curves of magnetite nanoparticles and hydrogels at room temperature. (**b**) Effect of pH on the Pb(II) ion uptake by m-CS/PVA and m-CS/PVA/CCNFs hydrogels. Adsorption isotherms (**c**) and adsorption kinetics (**d**) of Pb(II) ion uptake on m-CS/PVA and m-CS/PVA/CCNFs hydrogels. The inset shows the fitting results by the Langmuir isothermal model (**c**) and pseudo-second-order model (**d**)

HPC-M_oS_2/HPC hydrogels showed an enhanced adsorption behavior for methylene blue (Fig. 7a). The adsorption kinetics and isotherms were studied with different models. It indicated that the adsorption system followed predominantly the second-order rate model, and the adsorption process was mainly monolayer and took place on a homogeneous surface. More important, it could be reused to catalyze the degradation of methylene blue upon exposure to the sunlight as shown in Fig. 7b. The absorbed dyes in MoS_2-HPC/HPC hydrogels could be degraded upon exposure to sunlight, and then the hydrogels were circularly used to absorb dyes again. Considering the recycling properties of low-cost and biocompatible cellulose, the composite hydrogels will become promising candidates to remove dyes from effluents.

2.2 Drug-Selective Adsorption, Delivery, and Release

Hydrogels are hydrophilic polymer networks that can absorb more than 100 times their dry weight in water, giving the physical characteristics like soft tissue. In

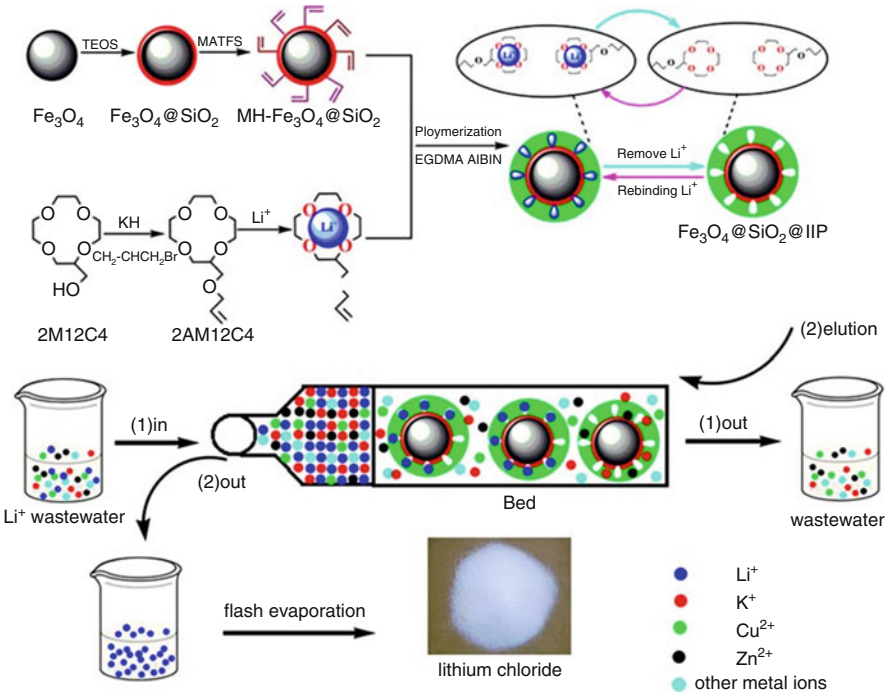

Fig. 5 Synthesis route for Fe_3O_4@SiO_2@ion-imprinted polymer

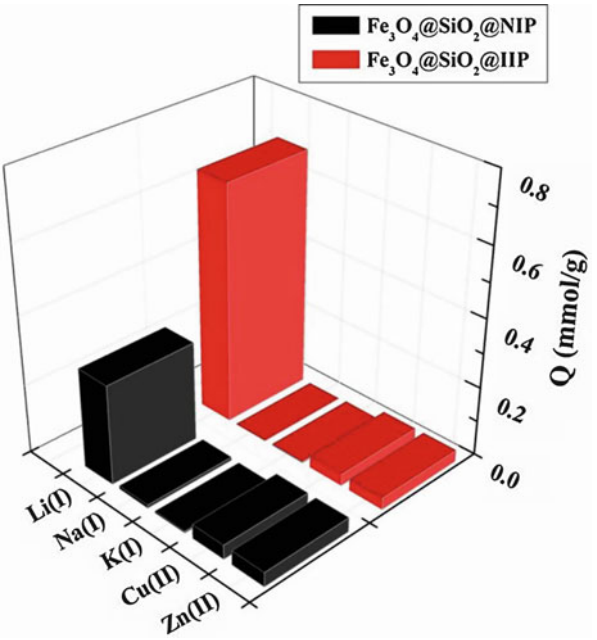

Fig. 6 Selective adsorption of Li(I) by Fe_3O_4@SiO_2@IIP and Fe_3O_4@SiO_2@NIP. Conditions: 50 mg of adsorbent, 50 mL of Li(I) with 10 mmol/L, and temperature of 25 °C

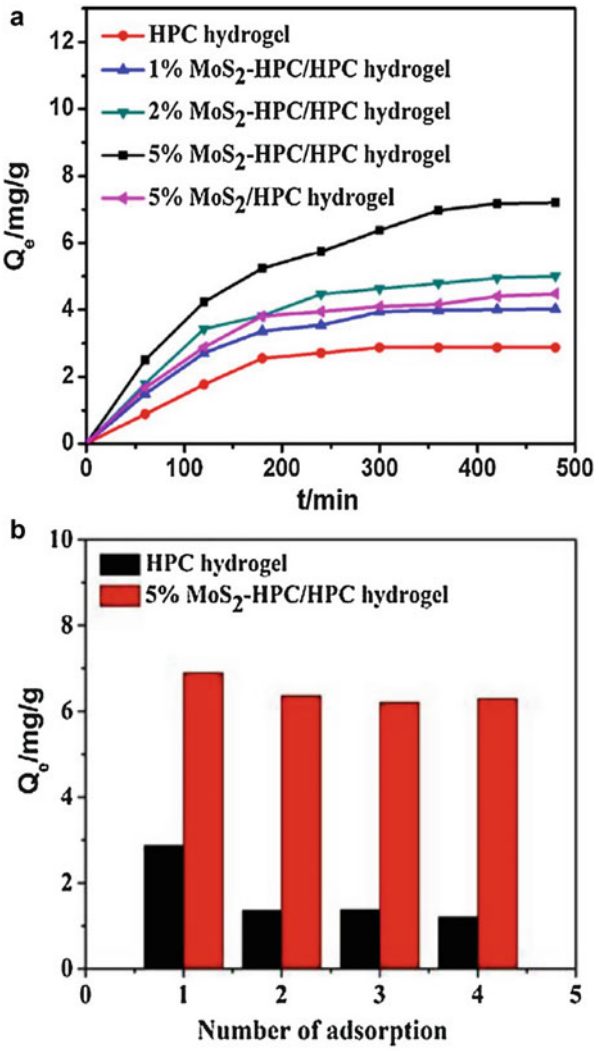

Fig. 7 (**a**) Time profile of methylene blue removal on hydrogel. The hydrogel was 0.19 g and the initial concentration of methylene blue was 50 ppm. (**b**) The photo-induced recycling properties of HPC hydrogel and 5% MoS2-HPC/HPC hydrogel

addition, hydrogels are highly permeable which facilitate exchanges of oxygen, nutrient, and other water-soluble metabolites. Thus, hydrogels are being investigated as drug delivery system due to their potential which can control the transport and release of macromolecular drugs such as pesticides [27–29], proteins [30–32], and nucleotides [33]. The diffusion mechanism of solute molecules within hydrogels is of great interest for a wide variety of industrial applications.

Recently, functional hydrogels are wildly studied in many fields, especially in drug delivery [34–36] and release aspects [37–39]. Molecularly imprinted magnetic cellulose microspheres (MIP-MCM) [40] were developed by a surface functional monomer-directing system. A layer of MIP was coated on the surface of the

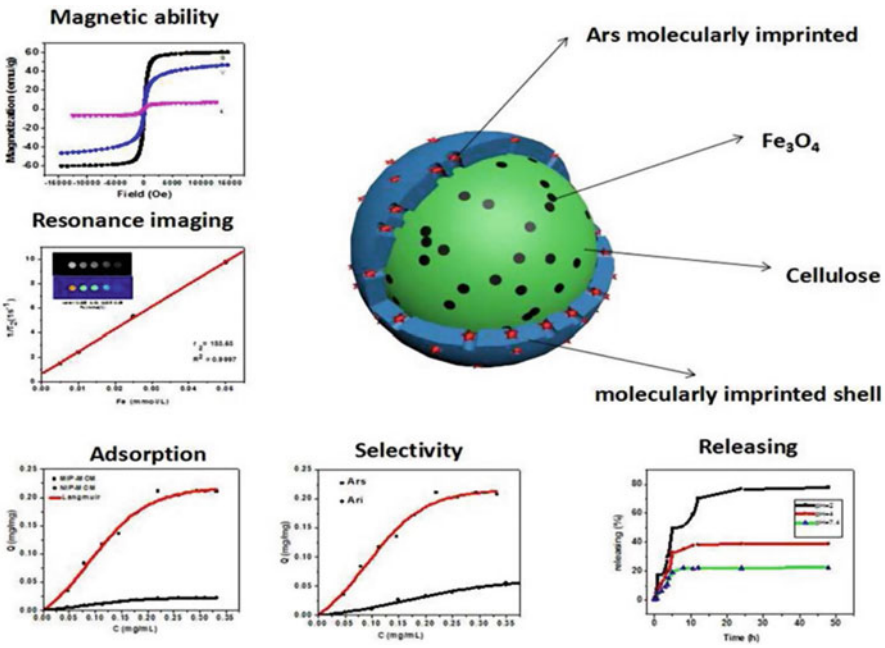

Fig. 8 Schematic procedure for molecularly imprinted magnetic cellulose microsphere preparation

cellulose microspheres in which Fe_3O_4 nanoparticles were embedded before. The process of preparation was shown in Fig. 8. By selecting artesunate (Ars) as template, the product showed high selectivity to Ars. Meanwhile, the MIP-MCM also showed highly regenerate and stable in wide pH and temperature ranges. The adsorption of Ars reached equilibrium within 10 h, and the maximum adsorption quantity was as high as 0.22 mg/mg. Through the Langmuir–Freundlich isotherm and pseudo-second-order kinetic model, the thermodynamic studies suggested that the adsorption of Ars on MIP-MCM was a spontaneous process. MIP-MCM also showed rapid magnetic separation and high reusability (retained 90% adsorption quantity after five cycles). Furthermore, MIP-MCM was good negative MRI contrast agents with good biocompatibility. Due to these properties, this work offered a new potential application for MIP-MCM in aspects of drug delivery, tracking, disease diagnosis, and therapy.

P(2-hydroxyethylmethacrylate/methacralic acid) hydrogels [41] were synthesized by gamma radiation-induced copolymerization of 2-hydroxyethylmethacrylate (HEMA) and methacrylic acid (MAA) in aqueous solution. The hydrogels as carrier for the drug adsorption and controlled release capacities of chlortetracycline HCl were investigated (see Fig. 9). The adsorption and release processes were stable in wide pH and temperature ranges. The influence of MAA content of hydrogels on the adsorption capacities was studied. The adsorption capacity of chlortetracycline HCl increased from 8 to 138 mg per gram dry gel with increasing amount of MAA in the gel system. The release of chlortetracycline HCl from the poly (HEMA/MAA)

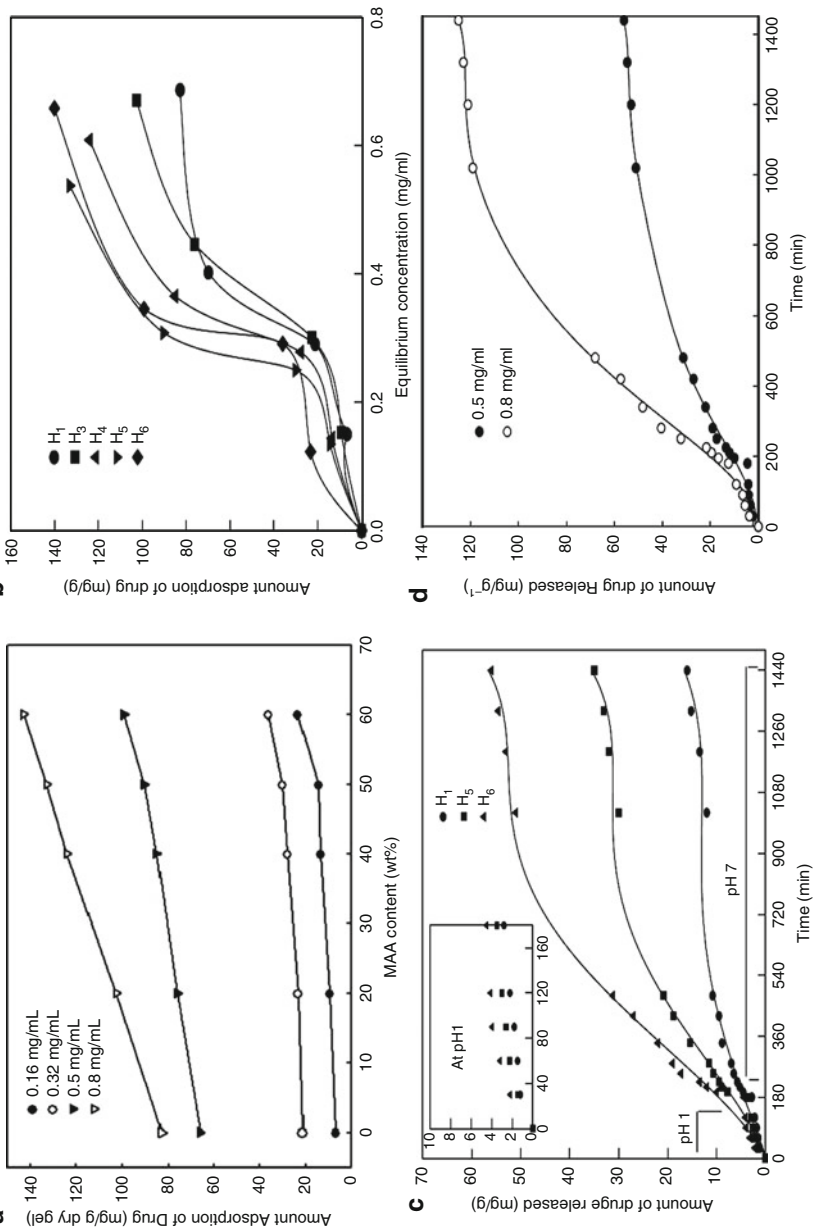

Fig. 9 (**a**) Effect of MAA content on the amount adsorption (mg/g) of (HEMA/MAA) hydrogels, at different drug concentrations. (**b**) Relationship between equilibrium concentration of chlortetracycline HCl and its amount adsorption (mg/g) for different (HEMA/MAA) compositions. (**c**) Chlortetracycline HCl

hydrogels, as studied at the physiological temperature of 37 °C, exhibited a strong pH-dependent release behavior, which offers minimum release at pH 1.0 and maximum release at pH 7–8.

3 Stimuli-Responsive Hydrogels

Stimuli-responsive hydrogels are a broad class of hydrogels whose swelling or deswelling processes, gel-to-solution or gel-to-solid transitions, and shapes can respond to the physical or chemical external stimuli, such as temperature, pH, magnetic, ultrasonic, electrochemistry, or light. Different kinds of stimuli-responsive hydrogels are used in various areas, like sensors [42, 43] and actuators, display and image devices [44–46], conditional controlled drug delivery [27–33], and so on. There are many different synthetic methods and sources to prepare stimuli-responsive hydrogels and exploit different applications.

3.1 pH- and Temperature-Sensitive Hydrogels

Temperature- and pH-sensitive hydrogels are most wildly investigated. Recently, some dual- even multi-stimuli-responsive hydrogels are developed. A novel poly((2-dimethylamino) ethyl methacrylate) PDMAEMA and poly ((2-dimethylamino) ethyl methacrylate-*co*-butyl methacrylate) P(DMAEMA-co-BMA) hydrogels were studied on the mechanical properties and pH- and temperature-sensitive swelling behaviors [47]. Mechanical measurements showed that the addition of hydrophobic comonomer butyl methacrylate (BMA) increased the mechanical strength of the network. Swelling studies showed that these hydrogels were both pH- and temperature-sensitive (see Figs. 10 and 11). It was possible to control the pH- or temperature-sensitive phase transition characteristics of these hydrogels without changing the chemical structure by a change in temperature or pH of the surrounding environments, respectively. Additionally, it also likely to further tailor the phase transition properties of the hydrogels by incorporation of a hydrophobic comonomer butyl methacrylate (BMA). Increasing the BMA content of the hydrogel chemical structure reduced the phase transition points of the temperature and pH.

Fig. 9 (continued) released from different (HEMA/MAA) compositions as a function of time, at two pH values (pH 1 at time up to 180 min and pH 7 at time above 180 min) and at constant concentration of drug 0.5 mg/ml. (**d**) Chlortetracycline HCl released from (HEMA/MAA) (40/60) hydrogels as a function of time for different loaded amounts of drug, at two pH values (pH 1 at time up to 180 min and pH 7 at time above 180 min)

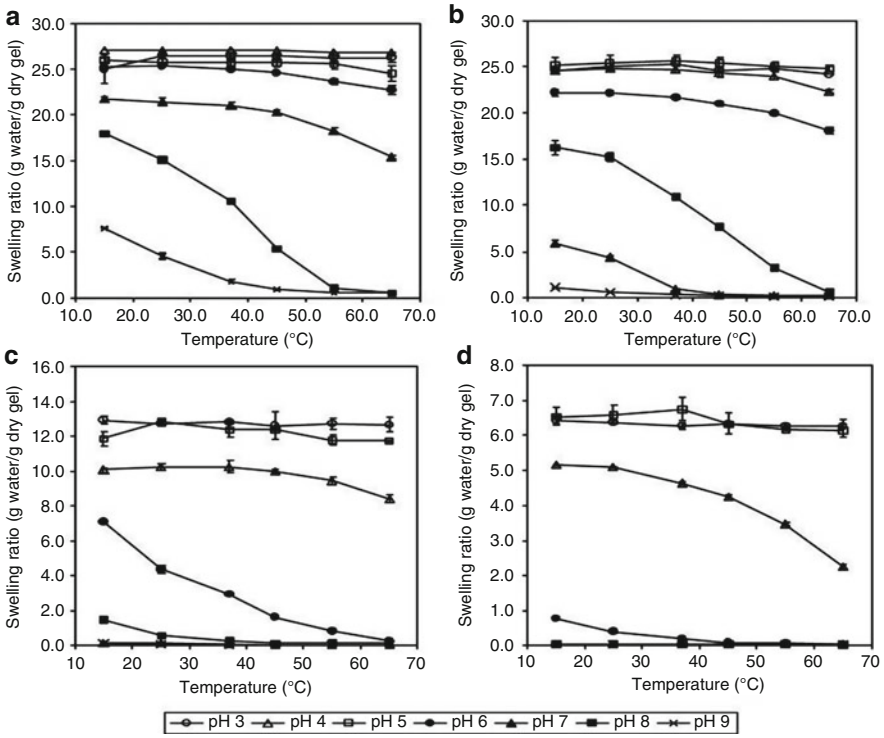

Fig. 10 Swelling ratio of the poly((2-dimethylamino) ethyl methacrylate-*co*-butyl methacrylate) hydrogels as a function of temperature at different values of pH. (**a**) 0% butyl methacrylate; (**b**) 20% butyl methacrylate; (**c**) 40% butyl methacrylate; (**d**) 60% butyl methacrylate

3.2 Light-Sensitive Hydrogels

Due to their remotely triggerable releasing ability and combinational functionalities, light-responsive hydrogel particles are applied in microreactor, drug delivery, and tissue engineering. Light stimuli can be used for remote and noninvasive switching of the therapeutic agents' flux. Near-infrared (NIR) light can penetrate body tissue with limited absorbance. Thus, NIR light-responsive hydrogel particles with desirable compartmental structures were produced using suspended agarose/alginate pre-gel droplets induced by a superhydrophobic surface as templates [48] as shown in Fig. 12. The agarose/alginate double-network hydrogel was synthesized via a two-step sequential gelation process. The synthesized hydrogel particles, when loaded with polypyrrole (PPy) nanoparticles that act as photothermal nanotransducers, were demonstrated to function as near-infrared (NIR) light triggerable and deformation-free hydrogel materials. Compared with the massive release of tetramethyl rhodamine isothiocyanate (TRITC)-dextran (≈45%) from the single-compartmental particles induced by laser irradiation for 10 min, the release process was controlled and regulated to deliver 25% of the TRITC-dextran from the core-

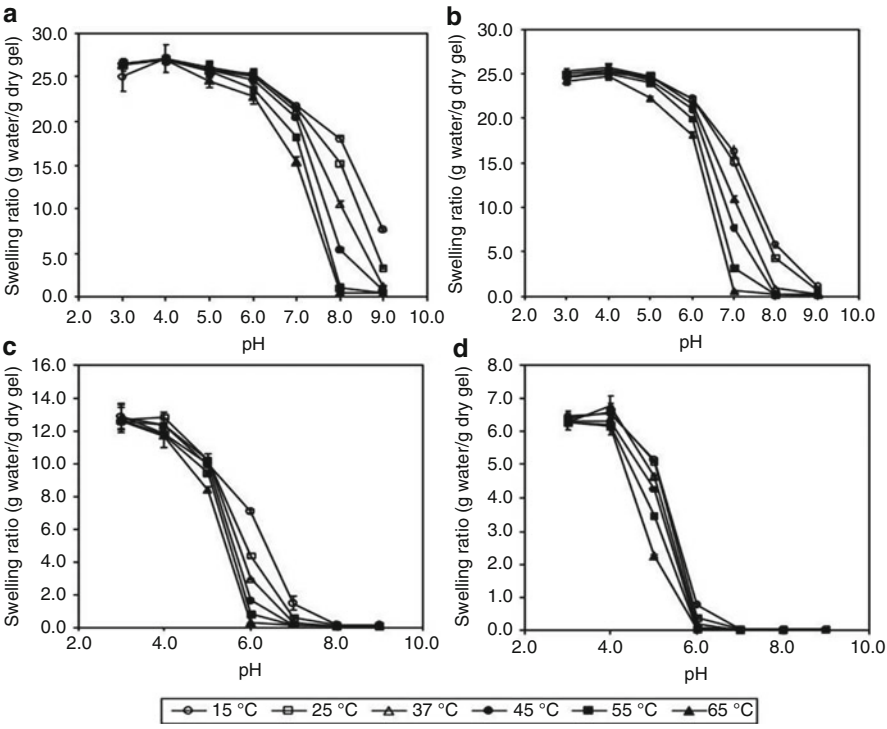

Fig. 11 Swelling ratio of the poly((2-dimethylamino) ethyl methacrylate-*co*-butyl methacrylate) hydrogels as a function of pH at different temperatures. (**a**) 0% butyl methacrylate; (**b**) 20% butyl methacrylate; (**c**) 40% butyl methacrylate; (**d**) 60% butyl methacrylate

shell structured particles. These multi-compartmental hydrogel particles exhibited tailored properties such as tunable particle size, tunable layer thickness, tunable layer number, and selective light sensitivity, which provided a wide range of options for drug encapsulation and remotely controlled release.

3.3 Electric-Sensitive Hydrogels

In recent years, capacitors have been extensively explored as an electrochemical device. The electrode materials are usually coated on the surfaces of current-collecting electrodes. The traditional current-collecting electrodes such as platinum, gold, or titanium are very expensive. The double-layer charges in thick electrode materials cannot be conveniently transferred to current-collecting electrodes (CCEs) and decrease the rate capability of electrochemical capacitors (ECs) with thick electrodes. A graphene hydrogel/nickel foam (G-Gel/NF) composite electrode was prepared by depositing reduced graphene oxide in the micropores of

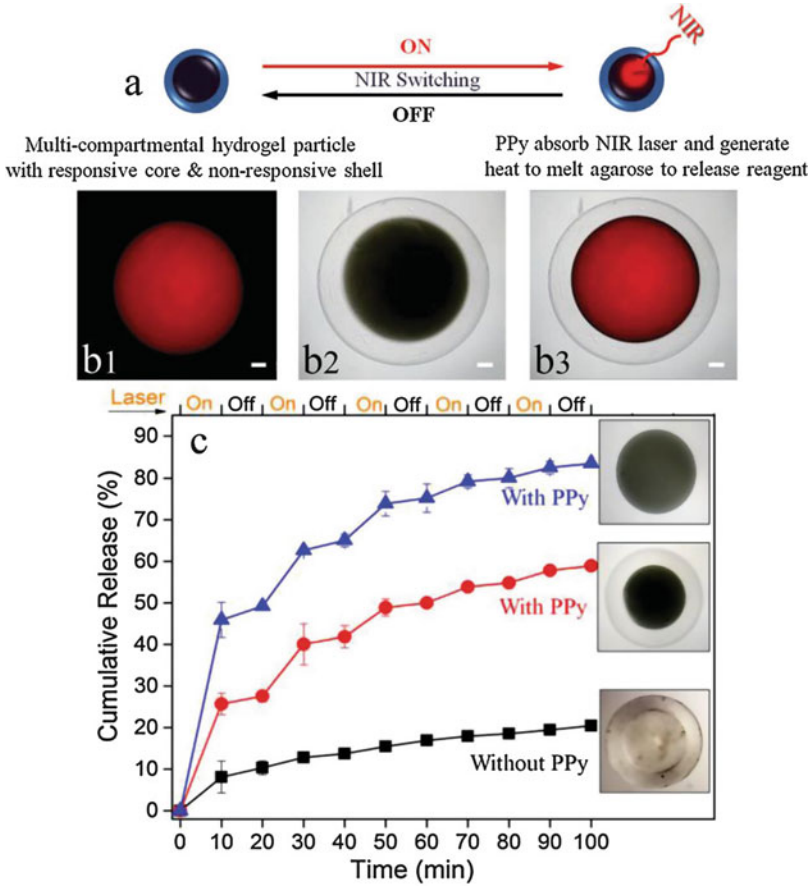

Fig. 12 (**a**) Schematic illustrations showing NIR laser-induced TRITC-dextran released from the multi-compartmental hydrogel particles with a core-shell structure, in which the PPy nanoparticles and the TRITC-dextran-loaded core exhibited NIR laser sensitivity, whereas the non-loaded shell was not responsive to NIR stimulation. (**b1**–**b3**) Microscope observation showing the multi-compartmental hydrogel particles with a core-shell structure, in which (**b1**) was a fluorescent microscope picture indicating the loading of TRITC-dextran in the hydrogel core, (**b2**) was a bright-field microscope picture indicating the loading of PPy nanoparticles in the hydrogel core, and (**b3**) was the overlay of (**b1**, **b2**) to indicate the multi-compartmental hydrogel particle with a loaded core and non-loaded shell. (**c**) NIR laser-induced release of TRITC-dextran from the hydrogel particles; the scale bar was 200 μm

nickel foam [49]. In this case, a thick (1.0 mm) G-Gel was separated into small pieces on the micrometer scale, and each of them was surrounded by Ni framework. Thus, the distances of ion/electron transportation in the electrodes were shortened. Consequently, the ECs based on thick G-Gel/NF electrodes (G-Gel/NF ECs) exhibited high specific capacitances (in terms of area), long durability, and high rate capability as shown in Fig. 13. Therefore, the G-Gel/NF electrodes not only

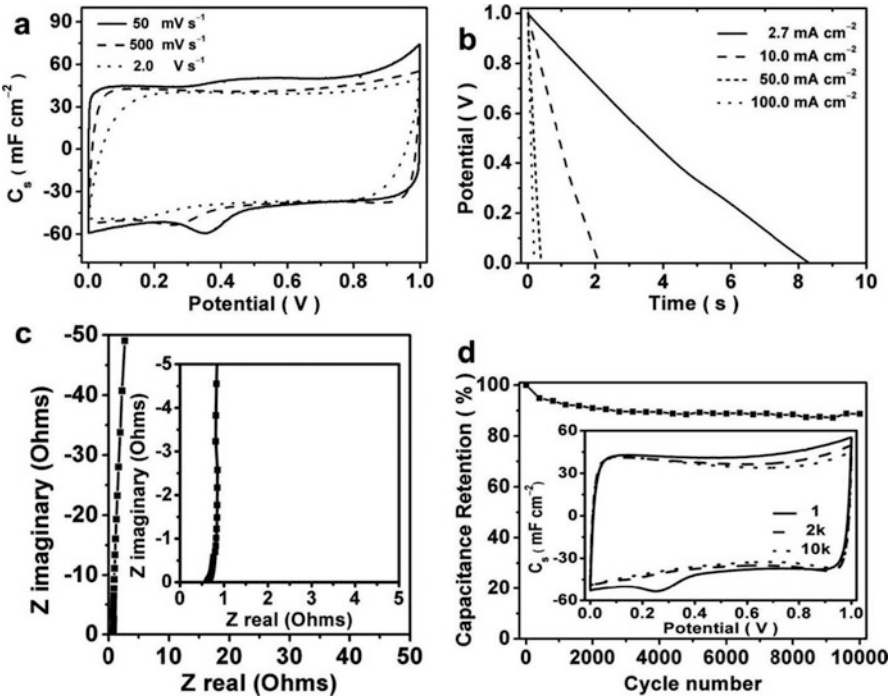

Fig. 13 (**a**) CV curves of G-Gel/NF EC in 5 M KOH at different scan rates. (**b**) Discharge curves of G-Gel/NF EC at different current densities. (**c**) Nyquist plot of G-Gel/NF EC. Inset: Plot on an enlarged scale. (**d**) Cycling stability of G-Gel/NF EC upon charging/discharging at a current density of 10 mA cm^{-2}. Inset: CV curves recorded before and after charging/discharging for 2000 or 10,000 cycles; scan rate = 500 mV s^{-1}

exhibited large specific capacitance and long cycling life but also showed high rate performance. By this way, the graphene material and current-collecting electrode were built in one piece without occupying additional volume. Furthermore, the micropores of G-Gel were exposed to the electrolyte for the access of ions to form electrochemical double layers, and the nickel framework shortened the distances of charge transfer.

An interpenetrating polymer networks (IPNs) composed of hyaluronic acid (HA) and poly(vinyl alcohol) (PVA) hydrogels [50] were prepared, and the effects of various pH conditions and electric field on swelling ability were investigated. The IPN hydrogels exhibited pH-sensitive and electro-responsive properties (see Fig. 14). The IPN hydrogels exhibited a relatively high swelling ratio as HA content is increasing. The HA–PVA (3:1, wt%) sample containing the highest HA content among samples showed the highest swelling ratio of pH-dependent swelling behaviors. IPN hydrogels showed electro-responsiveness as shrinking and expanding reversibly with the on–off switching of the electric field. HA–PVA IPN hydrogel showed the greatest electro-responsiveness volume change with the composition of HA–PVA (1:1, wt%).

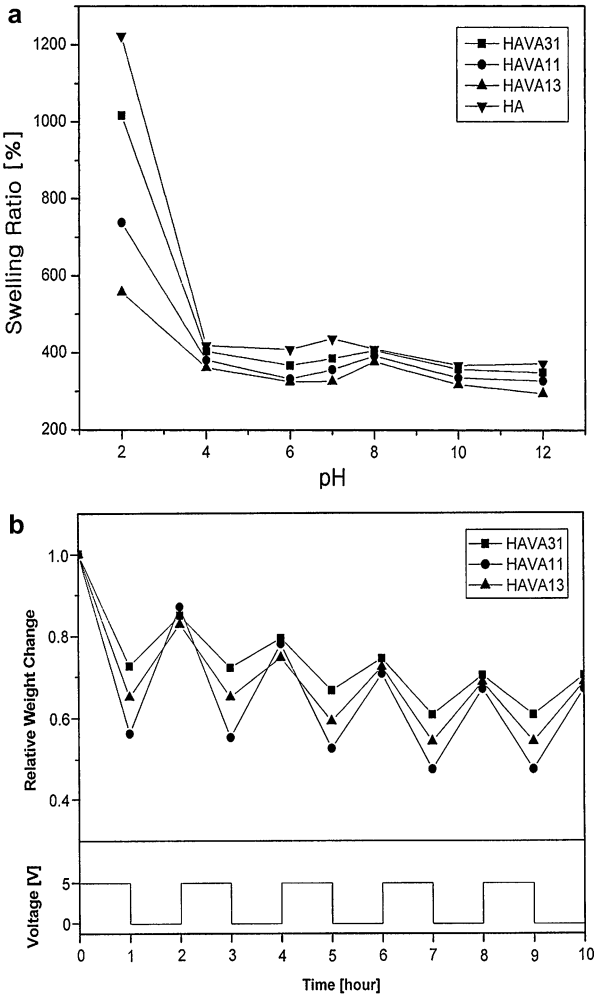

Fig. 14 (**a**) pH-dependent swelling behavior of HA–PVA IPN hydrogels. (**b**) Electro-responsiveness of HA–PVA IPN hydrogels due to on–off switching of electric field (5 V). HA–PVA (1:1, wt%), HA–PVA (1:3, wt%), HA–PVA (3:1, wt%)

3.4 Dissolving Hydrogels

The controllable dissolving hydrogel is another trigger. By external stimuli, the hydrogel can undergo gel-to-solution or reversible phase transitions. On-demand dissolution biocompatible hydrogels [51] were synthesized by thiol−thioester exchanging reactive groups as functional units for aqueous dissolution. When hydrogels was stimulated in water, the thiol−thioester could hydrolyze. The rates of exchange and hydrolysis depended on the temperature and pH of the solvent. The dissolution of thiol−thioester hydrogels was shown in Fig. 15. These hydrogels could be applied as wound dressings which would provide service as a protective barrier against bacterial infection. The management and closure of wounds after traumatic injury or surgical intervention are of significant clinical importance.

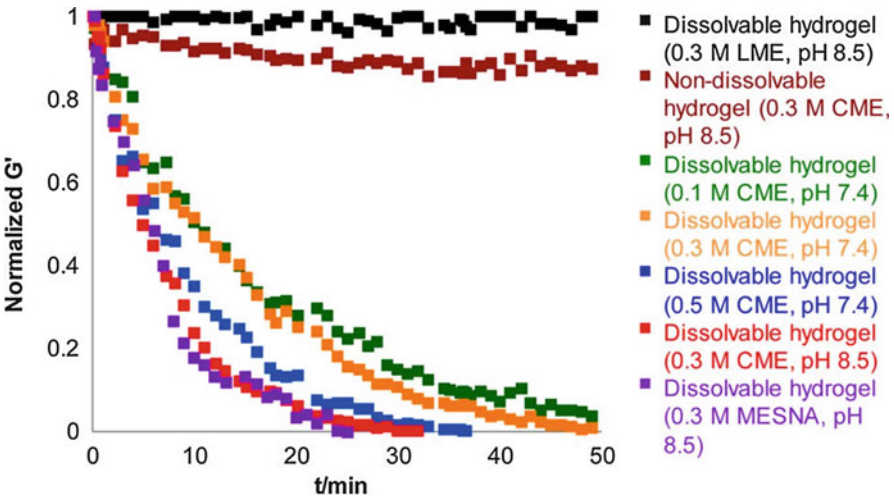

Fig. 15 Hydrogel dissolution as monitored by rheometry

Stimuli-responsive hydrogels that function as sealants, adhesives, or dressings are emerging as vital alternatives to current standards of care that rely upon conventional sutures, staples, or dressings.

3.5 Shape Memory Hydrogels

The "shape memory" effect is defined as an elastic deformation (programming) of a sample into a temporary shape stabilized by reversible covalent or physical cross-links. Shape memory hydrogels can form into a temporary shape and recover the original shape by external stimuli such as temperature, light, pH, or electricity. Based on the biocompatibility, the hydrogels have many biomedical or sensory applications, such as smart medical devices, implants for minimally invasive surgery, and heat-shrinkable tubing or films. The new shape memory hydrogels [52] sensitive to Fe^{3+}, pH, and temperature with tunable mechanical properties were presented in Fig. 16. Three programmable reversible systems including PBA-diol ester bonds (the reversible PBA-diol ester bonds formed by phenylboronic acid groups (PBA) and adjacent hydroxyl groups of glucosamine), AAc–Fe^{3+} (the coordination interactions between acrylic acid (AAc) and Fe^{3+} ions), and coil−helix transition of agar were applied to memorize temporary shapes and endowed the hydrogels with outstanding multishape memory functionalities.

3.6 DNA Hydrogels

Except normal materials, DNA, RNA, or nucleic acids also can be introduced into composite hydrogels as functional components. DNA can be precisely designed with

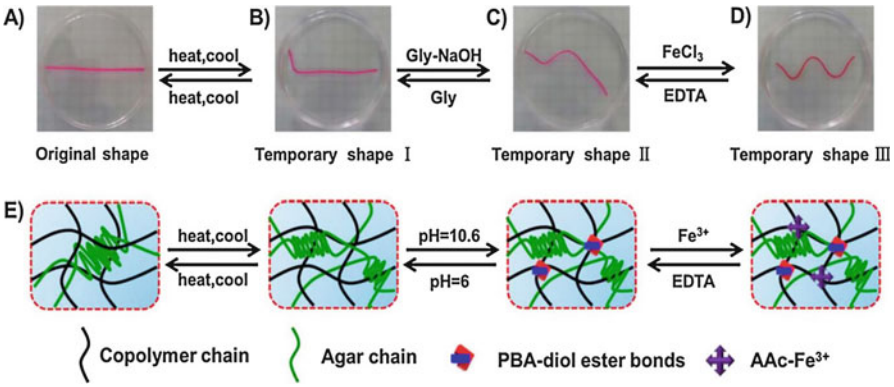

Fig. 16 Fe^{3+}, pH, and thermo-induced multishape memory effect. (**a**, **b**) Temporary shape I was fixed by coil–helix transition of agar upon changing the temperature. (**b**, **c**) Cross-links of dynamic PBA-diol ester bonds can be applied for memorizing temporary shape II. (**c**, **d**) Through the chelation between Fe^{3+} and carboxylic groups, temporary shape III can be fixed. (**e**) Mechanism of programmed multishape memory process

specific sequences and self-assemble into two- or three-dimensional structure to assemble nanoparticles. Through the cross-linked networks of DNA assembly, DNA hydrogels have great potential applications in biomaterials, such as drug and gene delivery, biosensing, and tissue engineering. In the past few years, many DNA hydrogels have been reported. The driving forces of the DNA hydrogels are physical interaction and chemical interaction. For physical interaction, DNA directly extracted from the nucleus in nature, like a long linear polymer, and formed a hydrogel via physical entanglement or by chemical cross-linking of small molecules. For chemical modification, DNA could be covalently grafted onto synthetic polymers and served as a cross-linker. The recognition of complementary DNA strands led to cross-linking of polymer chains and caused hydrogel formation.

A new and general platform created pure DNA hydrogels [53] through self-assembly as shown in Fig. 17. Two building blocks, a Y-scaffold and a linker, led to hydrogel formation. Moreover, by tailoring the DNA building blocks, the DNA hydrogels formed rapidly without any chemical treatment. The formation mechanism and properties of the DNA hydrogels were systematically studied. The DNA hydrogels reversibly responded to thermal stimulus, by switching between the gel and sol state across a transition temperature, as well as respond to enzymes when restriction sites are inserted into one of the building blocks. Therefore, it provided a new class of intelligent materials for a diverse range of biological and biomedical applications.

3.7 RNA Hydrogels

According to the self-assembled three-dimensional structures of oligonucleotides, it has showed promising applicability for imaging and gene delivery mainly using siRNAs. A novel RNA-triple-helix hydrogels [54] was prepared through programmable self-assembly of the two miR sequences to provide a stable and efficient nanovehicle for

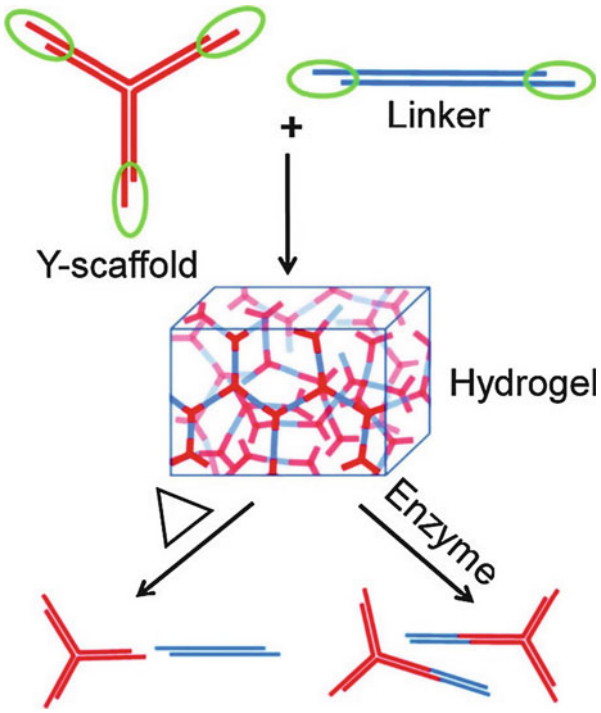

Fig. 17 Schematic representation of DNA hydrogel formation. The Y-scaffold and linker are designed to cross-link by hybridization of their "sticky ends" (emphasized by green circles). By tailoring these "sticky ends" and inserting restriction sites in the linker sequences, the DNA hydrogels show thermal and enzymatic responsive properties

in vivo miR local delivery (see Fig. 18). Conjugating the RNA triple helix to dendrimer (triplex nanoparticles) formed an adhesive hydrogel upon mixing with dextran aldehyde controlled release of the two miRs. The RNA-triple-helix hydrogels was consisted of stable two-pair FRET donor/quencher RNA oligonucleotides.

Self-assembled RNA-triple-helix conjugates remained functional in vitro with high selective uptake and controlled over miRNA expression compared with their respective single-stranded or double-stranded forms (Fig. 19). This method provided a novel strategy for concomitant on miRNA inhibition and tumor suppressor miRNA replacement therapy using a RNA-triple-helix hydrogel scaffold that afforded highly efficacious local anticancer therapy. Hence, cancer gene delivery systems should provide potent, selective, and specific treatment to tumor cells only, unlike the standard delivery of most conventional chemotherapeutic drugs. This approach can be implemented to design self-assembled triplex structures from any other miR combination, or from other genetic materials, including antisense DNA or siRNA, to treat a range of diseases.

4 Self-Healing Hydrogels

Self-healing is one of the most remarkable properties of biological materials. The special ability of natural materials to heal cracks often involves an energy dissipation mechanism due to the so-called sacrificial bonds that break and reform dynamically

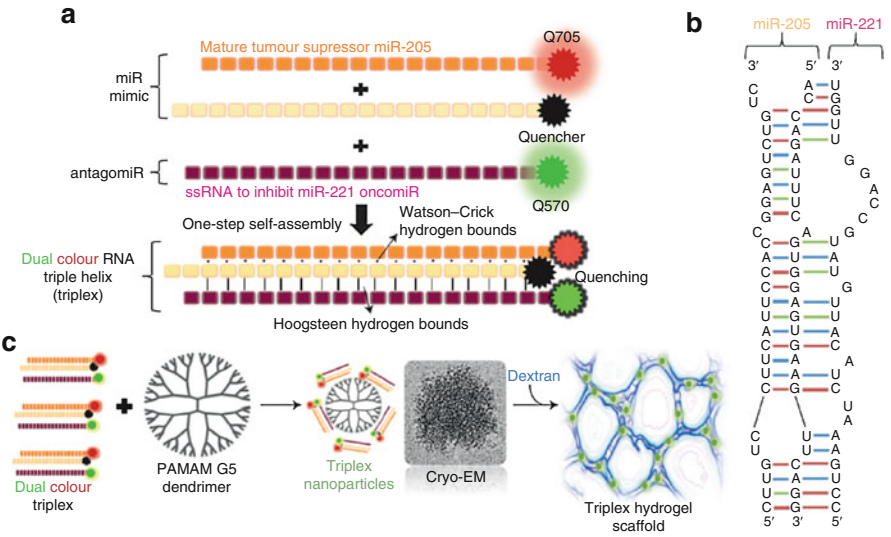

Fig. 18 Self-assembled RNA-triple-helix hydrogel nanoconjugates and scaffold for microRNA delivery. (**a**) Schematic showing the self-assembly process of three RNA strands to form a dual-color RNA triple helix. The RNA triplex nanoparticles consist of stable two-pair FRET donor/quencher RNA oligonucleotides used for in vivo miRNA inhibition (miR-221 antagomiR) strategy and miRNA replacement therapy (miR-205 mimic). (**b**) Secondary structure of an RNA triple helix bearing both miR-205 mimic and miR-221 antagomiR (structure produced/adapted using M-fold software). (**c**) Formation of the RNA-triple-helix hydrogel scaffolds by conjugation of the RNA-triple-helix structure to PAMAM G5 (Cryo-EM image showing the branched spongelike nanoscopic structure) followed by reaction with oxidized dextran to form the adhesive hydrogel

before the fracture of the molecular backbone. Numerous studies have been conducted in recent years to improve the mechanical performance of hydrogels. The self-healing materials which are capable of recovering their original mechanical performance after fracture require intermolecular non-covalent interactions. Although synthetic hydrogels are very similar to biological tissues, they are normally very brittle and lack the ability to self-heal, which hinders their use in any stress-bearing applications.

As new functional materials, self-healing hydrogels are under vast research nowadays for drug delivery, 3D cell proliferation, and tissue engineering. The broken self-healing hydrogels after damaged can regenerate the integral network and stay at the target position, enhancing the medicine delivery efficiency. This property can be introduced into macromolecules by the hydrogen bond driven through the creation of specific non-covalent intermolecular interactions. Moreover, self-healing systems can repair themselves autonomously, restoring the initial structures and functions without external stimulus after the interior or exterior cracks, which is similar to the ability of some living organisms (e.g., human skin). Constructing a non-covalently bonded system is an efficient approach to preparing self-healable polymeric hydrogels. Thus, introducing the self-healing feature to the

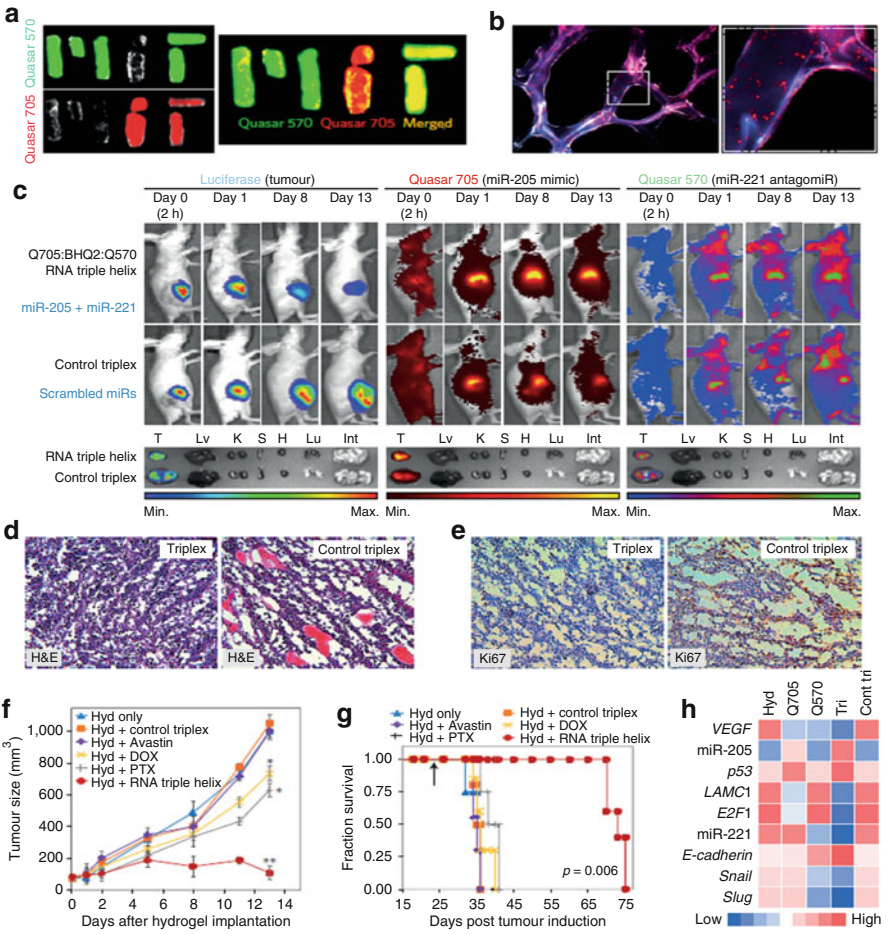

Fig. 19 In vivo miRNA modulation and tumor therapy via RNA-triple-helix hydrogel scaffolds. (**a**) Dual-color hydrogel scaffolds made of RNA-triple-helix nanoconjugates preincubated with complementary miR targets. (**b**) Cryosection of dendrimer–dextran adhesive hydrogel (12 μm thickness) depicting adhesive morphology (dextran aldehyde was tagged with Alexa Fluor 405). Red spots represent the triple-helix nanoparticles containing Q705 (red) and Q570 (green) oligonucleotides. (**c**) Live imaging of female SCID hairless congenic mice with triple-negative breast tumor xenograft implanted with hydrogels embedded with RNA-triple-helix nanoparticles and with a control triplex (scrambled miRs) (*n*D5 per group). Ex vivo images of breast tumors and whole body organs (T, tumor; Lv, liver; K, kidneys; S, spleen; H, heart; Lu, lung; Int, intestines) are also presented. (**d**) Hematoxylin and eosin (H&E) stains of tumors from treated groups with hydrogels embedded with RNA-triple-helix nanoparticles and with a control triplex (scrambled miRs). (**e**) Immunohistochemical evaluation of tumors treated with hydrogels embedded with RNA-triple-helix nanoparticles and with a control triplex for Ki67 to evaluate tumor cell proliferation. (**f**) Tumor size following treatment (*n*D5, statistical analysis performed with a two-way ANOVA, $**$, $P < 0.01$; $*$, $P < 0.05$). Individual tumors were measured using a Vernier caliper, and tumor volume was calculated by tumor volume (mm3) D width × (length2)/2. (**g**) Kaplan–Meier curves for mice treated with hydrogel scaffolds loaded with triple-helix and control triple-helix nanoparticles, as

hydrogel can improve the functionality and extend the application range of the hydrogel.

4.1 Self-Healing Hydrogels (Imine Bonds)

A straightforward method was used to prepare magnetic self-healing hydrogels by facilely mixing carboxyl-modified Fe_3O_4 nanoparticles in the self-healing hydrogels [55]. Due to the interaction between -NH_2 on chitosan and carboxyl groups on the Fe_3O_4 surface, the Fe_3O_4 nanoparticles could be dispersed well in chitosan solution to form a stable ferrofluid. This chitosan–Fe_3O_4 ferrofluid was subsequently mixed with difunctional poly(ethylene glycol) DF-PEG aqueous solution to quickly generate the target magnetic hydrogel. The chitosan–PEG hydrogels could form quickly through dynamic Schiff-base cross-linkage between amine groups of chitosan and benzaldehyde groups on DF-PEG termini. It was noticeable that the hydrogels healed itself automatically without any external stimuli. Figure 20 demonstrated the excellent self-healing capacity. This novel magnetic seal-healing hydrogel might have potential to be used in biological, medical, and environmental fields.

4.2 Self-Healing Hydrogels (Host–Guest)

Cyclodextrins (CDs) are water-soluble cyclic oligomers of D-(+)-glucose units bound to each other through α-1,4-glucose bonding. CDs of 6, 7, and 8 glucose units are called α-, β-, and γ-CDs, respectively. CDs can interact selectively with hydrophobic compounds of a size and shape matching their cavities to form inclusion complexes. Thus, many supramolecular hydrogels based on CDs inclusion complex with guest-containing polymers have been prepared. Self-healing properties of those based on host–guest interactions have been addressed. This work provided a novel supramolecular hydrogels [56] made of copolymers of *N*,*N*′-dimethylacrylamide (DMA) modified with cholic acid (CA, the most abundant bile acid in humans and many other species) and β-CD, respectively (Fig. 21). The dynamically reversible host−guest complexation built reasonably good mechanical properties of the cross-linked polymer network. The natural origin of the constituents made the hydrogels suitable candidates for biomedical applications.

Fig. 19 (continued) well as for the drugs (DOX, PTX, and Avastin). Statistical analysis (*n*D5) was performed with a Log-Rank Mantel–Cox test (*P*D0.006). Survival cutoff criteria included tumor ulceration or compassionate euthanasia, when the aggregate tumor burden >1 cm in diameter or if tumor impedes eating, urination, defecation, or ambulation. Arrow represents the day of hydrogel implantation (day 22 post tumor induction). (**h**) Heat-map summary of gene expression profiling of the miRs and their related genes that play key roles in cancer progression and migration

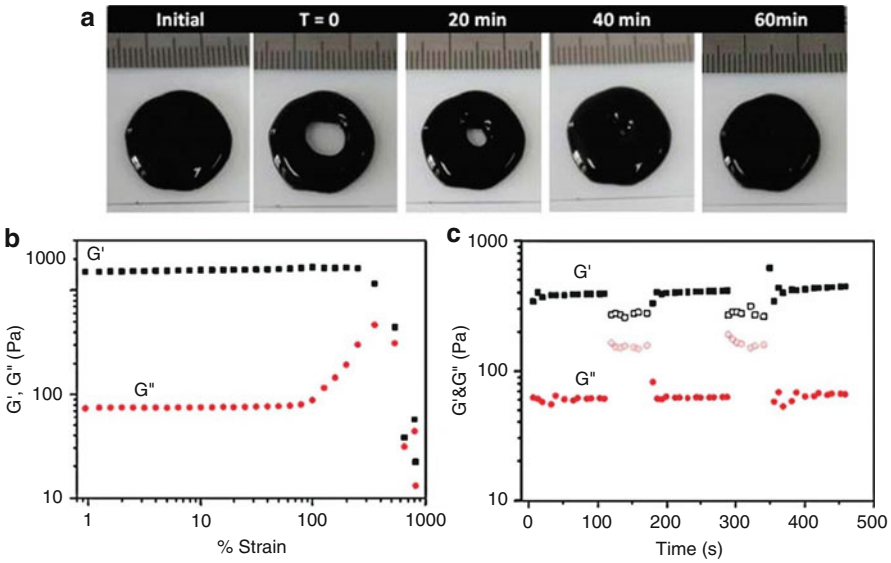

Fig. 20 (**a**) Photos taken during the self-healing process of the hydrogel. (**b**) Rheology analyses of the magnetic self-healing hydrogel. The storage moduli G′ and loss moduli G″ from strain amplitude sweep. (**c**) G′ and G″ from continuous strain sweep with alternate small oscillation force (g = 1% strain, solid dots) and large one (g = 200%, hollow dots)

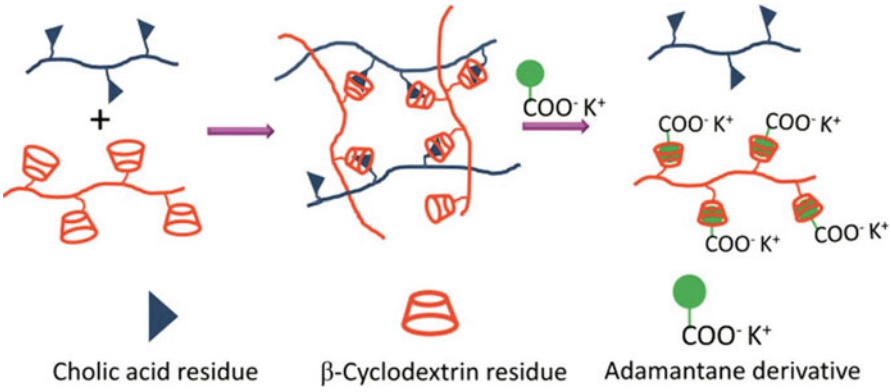

Fig. 21 Illustration of the formation of,P(*N*,*N*′-dimethylacrylamide-cholic acid-based methacrylate monomer)/P(*N*,*N*′-dimethylacrylamide-p-nitrophenyl acrylate and amino-CD) hydrogel and its dissociation triggered by the addition of potassium 1-adamantylcarboxylate (K-Ada)

4.3 Self-Healing Hydrogels (Hydrogen Bonds)

A series of novel self-healing pH-sensitive biodegradable hydrogels [57] based on cytosine- (C) and guanosine (G)-modified hyaluronic acid (HA) were prepared via hydrogen bonding under physiological conditions, with 1,6-hexamethylenediamine

(HMDA) as a bridging unit between nucleobase and HA. The lowest gel concentration, gelling time, pH-sensitivity, self-healing behavior, rheological properties, morphology, swelling ratio, degradation kinetics, and drug delivery behavior of HA-HMDA-C, HA-HMDA-G, and HA-HMDA-C/G hydrogels were investigated. As shown in Fig. 22, the series of pH-responsive self-healing hydrogels exhibited suitable gelling time, good rheology properties, high swelling ratio, biodegradability, effective drug loading capacity, and sustained drug release ability under physiological conditions. More important, these hydrogels could be attractive candidates for short- and medium-term injectable drug delivery systems, tissue engineering, cell scaffold materials, and regenerative medicine.

4.4 Self-Healing Hydrogels (Hydrophobic–Hydrophilic)

Hydrophobic interactions play a dominant role in the formation of large biological systems. These interactions can be generated in synthetic hydrogels by incorporation of hydrophobic sequences within the hydrophilic polymer network chains. The hydrogels [58] without a chemical cross-linker exhibited unique properties due to the strong hydrophobic interactions. They could only be dissolved in SDS solutions demonstrating the physical nature of cross-links. Results of dynamic light scattering and rheological and mechanical measurements showed that the hydrophobic associations between the blocks of stearyl methacrylate (C18) or dococyl acrylate (C22) units prevented water solubility and flow, while the dynamic nature of the junction zones provided homogeneity and self-healing properties together with a high degree of toughness. When fractured, the hydrogels formed using C18 associations could be repaired by bringing together fractured surfaces to self-heal at room temperature as shown in Fig. 23. The hydrogels without a chemical cross-linker exhibited unique properties. Strong hydrophobic associations between the blocks of C18 or C22 prevented dissolution in water and flow.

5 Conclusion

This chapter delivers a brief overview at functional hydrogels, especially adsorption hydrogels, stimuli-responsive hydrogels, and self-healing hydrogels. Due to the unique structure and properties, hydrogels can be used as adsorption materials for water treatment, drug separation and condition-controlled delivery system, sensors and actuators, and many other smart materials.

6 Future Scope

After decades of investigation, significant accomplishments in the development and characterization of hydrogels have been achieved, and the application of hydrogels has been spread to many aspects, such as green materials, new energy,

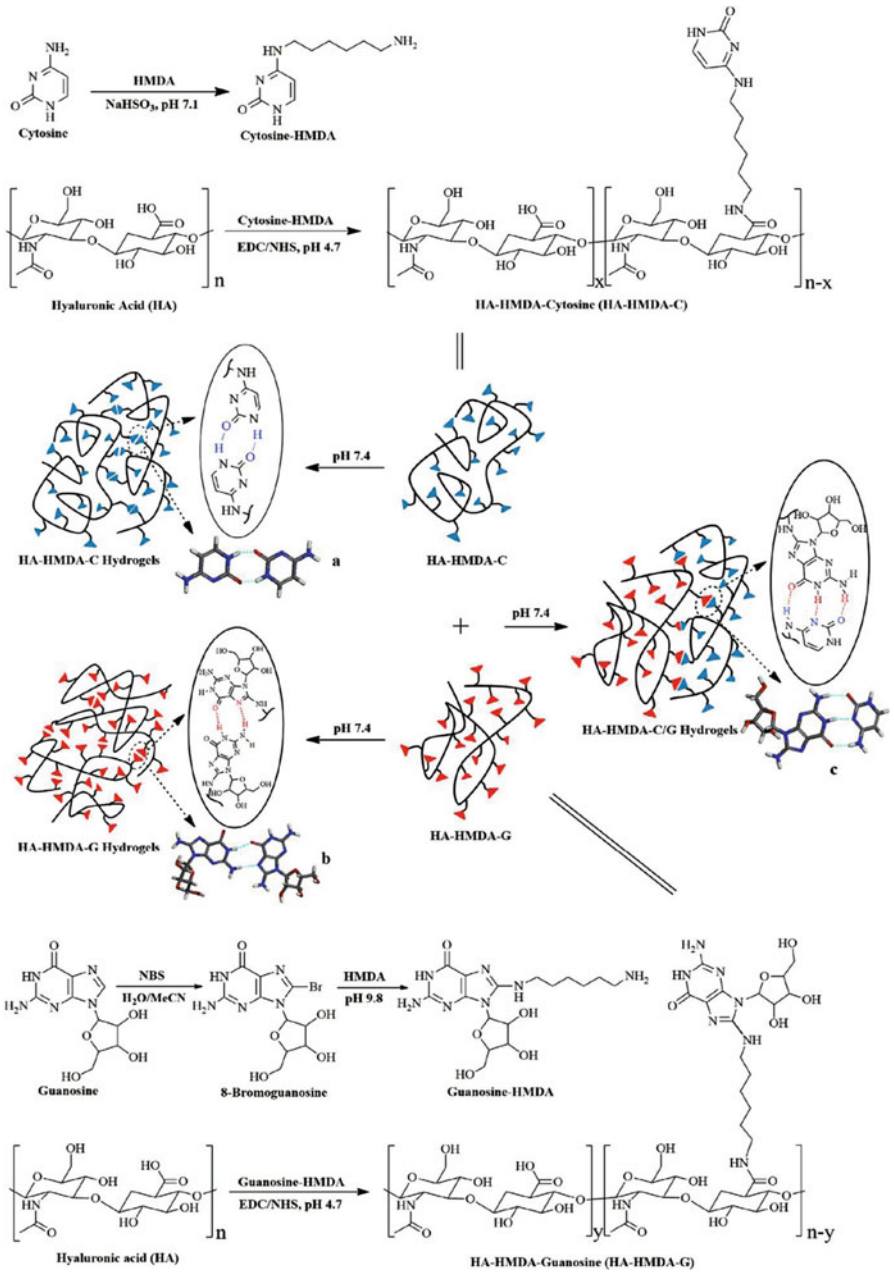

Fig. 22 Schematic illustration of synthesis routes of HA-HMDA-C and HA-HMDA-G and the formation of modified HA hydrogels via hydrogen bonding. The sketches of hydrogen bonds between cytosine and guanosine themselves or each other were carried out by computer simulations using Materials Studio 5.0 (Accelrys, San Diego, USA): (*a*) cytosines, (*b*) guanosines, and (*c*) cytosine and guanosine

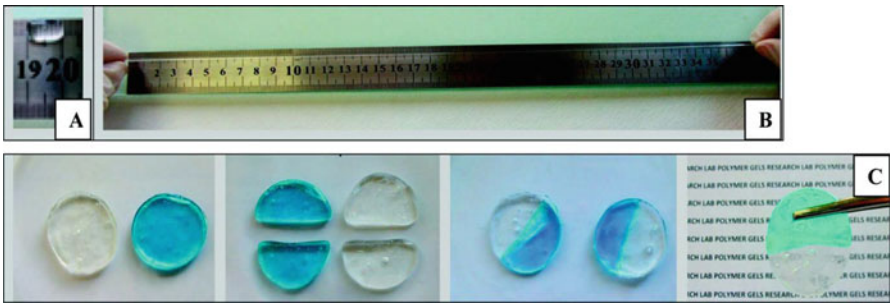

Fig. 23 Photographs before (**a**) and after stretching of a hydrogel sample formed in 0.5 M NaCl (**b**). (**c**) Photographs of two hydrogel samples formed in 0.5 M NaCl. One of the gel samples is colored with methylene blue for clarity. After cutting into two pieces and pressing the fractured surfaces together, they merge into a single piece

biomedicine, etc. The future hydrogels must be more and more smart. The trends of the hydrogel application would be on-demand deformation, artificial organs, wearable devices, etc. Meanwhile, more fundamental researches are necessary to make clear the mechanism of the unique properties of hydrogels.

Acknowledgments The authors acknowledge East China Normal University for providing research facilities and platform.

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Part II

Synthesis of Cellulose-Based Hydrogels

Synthesis of Cellulose-Based Hydrogels: Preparation, Formation, Mixture, and Modification

14

Neslihan Kayra and Ali Özhan Aytekin

Contents

Abstract

Cellulose is the most abundant biopolymer, and it has been used in different areas because of its unique properties as various fibril structures and sizes that affect

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tensile characteristic of the polymer. To increase its features and/or add a new property to cellulose, preparation and modification methods have been deeply investigated and reported. This chapter is classified into four different sections: preparation, formation, mixture, and modifications of cellulose. The preparation method of cellulose (including bacterial cellulose) is important, because it directly effects to fibril formation and structure. In addition to this, depending on usage area, cellulose is necessary to prepare as whisker, fibril, and nano-formations to sustain desired polymer structure. To increase the targeted property of cellulose hydrogel, different kinds of polymers such as polyvinyl alcohol and polyethylene glycol are mixed with cellulose during the preparation of hydrogel. However, cellulose hydrogels still need to improve its physical abilities. Therefore, various modifications have been developed for cellulose and its hydrogel. The most fundamental derivatives are methyl cellulose, hydroxypropyl cellulose, and carboxymethyl cellulose. In addition to this, in recent years, stimuli-responsive and superabsorbent polymers have become more popular. Swelling behavior of hydrogels can be changed by pH, temperature, composition of solvent, and electric field in stimuli-responsive polymers that are available to use in pharmaceutical, bioengineering, and tissue engineering areas. Superabsorbent hydrogels have the ability to absorb water up to several hundred times of their dried weight that can be used in bioengineering, agricultural, tissue engineering areas, and sanitary products. The reaction mechanisms and configurations of mixtures were clearly illustrated in this chapter. Groundbreaking and latest studies were discussed via the hydrogel properties based on analysis of X-ray diffraction (XRD), thermal gravimetric analysis (TGA), differential scanning calorimetry (DSC), Fourier transformation infrared spectroscopy (FTIR), tensile at break, tensile stress, and Young's modulus.

Keywords
Cellulose · Hydrogel · Cellulose nanocrystal · Cellulose nanofiber · Cellulose derivatives

1 Introduction

Cellulose is the most abundant biopolymer on Earth. The chemical structure of cellulose is based on repeating unit of glucopyranose sugar with β-(1–4) bindings (Fig. 1). Cellulose is one of the polymers that can be used in different areas because of its properties such as availability, crystallinity, molecular weight, and purity. The obtaining and production methods of cellulose are directly affecting stability and physical properties of it.

Cellulose is found with hemicellulose and lignin in plant. In addition to them, wax, pectin, and residual starch can be present in plant depending on plant type. The most common method for obtaining cellulose follows removal of these impurities using mechanical treatment and chemical treatments with sodium hydroxide [1] which is the most common chemical for cellulose purification. Reaction conditions

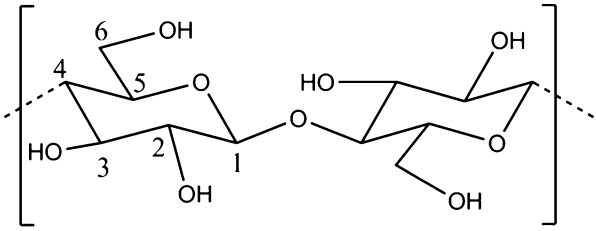

Fig. 1 Molecular structure of cellulose

are generally performed at mild conditions; however, the adjustment of reaction temperature and NaOH concentration is important to obtain highly pure and high degree of polymerization value [2]. Recently, new approaches such as pretreatment with ammonia, ultrasonication, and microwave treatments were proposed by researchers [3–5]. However, ultrasonication and microwave treatments are not suitable for large-scale processes especially for cellulose purification, because of their cost and productivity.

2 Preparation and Formation of Cellulose and Its Hydrogel

Cellulose is a linear-chain carbohydrate; it can be found as structural component of plants which is responsible for their mechanical strength or can be produced from fungi, algae, and bacteria.

Some specific features such as hydrophilicity, biodegradability, chirality, chain stiffness, chemical-modifying capacity due to extended hydroxyl groups, hydrolysis, and oxidation of chain-forming acetal groups and semicrystalline fiber structure make cellulose distinct and favorable among other polymers [6, 7]. Intermolecular reactions, crosslinking reactions, chain lengths and chain length distribution, and distribution of functional groups on repeating units are responsible factors from abovementioned characteristics of cellulose [6, 8].

The essential building blocks of cellulose are D-glucopyranose (glucose) units which are linked together with β-1,4-glycosidic bonds unlike the α-(1,4) glycosidic bonds which exist in other polysaccharide chains. After being linked, an anhydroglucose unit is formed, and two anhydroglucose units build up anhydrocellobiose (β-D-glucopyranose) which is the repeating unit of cellulose. Each anhydroglucose unit consists of six carbon atoms and three hydroxyl groups at C2, C3, and C6 atoms. These repeating β-D-glucopyranose molecules linked covalently together through acetal functions between the equatorial OH groups of C4 and the C1 carbon atoms. On cellulose chain, every second an anhydroglucose unit is rotated 180° in plane to adjust the acetal oxygen bridges angles [6, 8]. A D-glucose unit of cellulose chain includes the reducing end at C1 atom with free hemiacetal or aldehyde group and nonreducing end at C4 atom with free alcohol group [6, 8].

The chain length of cellulose polymer, degree of polymerization (DP), is defined as the number of anhydroglucose units in the polymer chain. Degree of

polymerization is dependent on source of cellulose and treatment of raw material [8] and is responsible for most properties of cellulose [9]. Although the degree of polymerization is different for each cellulose source, 20–30 repeating β (1,4)-linked glucan units exhibit all properties of cellulose [6].

Cellulose structure is semicrystalline that is composed of both crystalline (high-order) and amorphous (low-order) regions. The crystalline form of cellulose is attributed to extensive hydrogen bonds [6, 9]. Although crystallinity of the cellulose is affected by the source of the cellulose and isolation methods, generally degree of crystallinity is in the range of 40–70% [8]. Cellulose can present different types of crystalline structures due to location of hydrogen bonds between and within strands. Native cellulose includes cellulose I with structures Iα and Iβ, which exists dominantly in cellulose-produced bacteria, algae, and higher plants, respectively, and cellulose II exists mostly in structure of regenerated cellulose. Also, cellulose III and IV can be produced chemically. The conversion of cellulose I (metastable) to cellulose II (stable) is irreversible [9].

The morphological structure of cellulose consists of a system of fibrils which are elementary fibrils in 1.5- and 3.5-nm dimensions; microfibrils are built up by elementary fibrils with 10- and 30-nm dimensions, and microfibrillar bands are about 100 nm [6–8].

2.1 Nanocellulose

Different terminations might be used to define nanocellulose such as “cellulose that made up from nano sized fiber network with properties and functionalities determined nanofiber structure” [7] or “cellulose that has at least one dimension in nanoscale (1–100 nm)” [8] (Table 1).

Recently nanocellulose has attracted attention due to its specific chemical and physical features such as nanoporosity and transparency in their dispersion and composite forms [7], large surface area, capacity of surface chemical modifications [8], high surface area-to-volume ratio, high aspect ratio [10], and solubility in water [9] besides other important cellulosic properties.

Mainly classification of nanocelluloses is done according the cellulose source and preparation method. Nanocellulose particles can be produced by bacteria under controlled cultivation conditions, bacterial cellulose, or from plant or other sources of cellulose by disintegration methods either using mechanical forces, cellulose nanofibrils (CNF), or chemical substances and cellulose nanocrystals. While, production of nanocellulose via bio-formation is called bottom-up process, from disintegration methods it is called top-down process [8].

Nanocellulose-based hydrogel studies have been focused on the efficient separation of desired parts from whole cellulose with suitable pretreatments; sometimes modification of the surface of nanocellulose with various chemical reagents depends on target usage, finding appropriate and efficient hydrogel formation methods for incorporation of nanocellulose to polymer matrix with acting reinforcer.

Table 1 Different size values of cellulose formations

Cellulose formation	Source	Method	Length (nm)	Diameter (nm)	Reference
CNW	Cotton	Sulfuric acid hydrolysis	80–220	10–25	[11]
	Cellulose pulp	Sulfuric acid hydrolysis	258.5	35.2	[12]
	Microcrystalline cellulose (VIVAPUR 105)		210	5	[13]
	Wood		100–300	5–10	[14]
			158	45	[15]
CNC	Wood		100–300	3–10	[13]
			100–300	3–5	[16]
CNF			1000	3–10	[16]
			200–2200	3.5–20	[17]
			>1000	4	[18]
			500–2000	4–20	[19]
BC			1000–10,000	10–90	[20]

2.1.1 Cellulose Nanocrystals

Cellulose nanocrystals (CNC) or nanocrystalline cellulose (NCC) also described as crystal nanowhiskers are generally produced via acid hydrolysis treatment such as sulfuric acid or hydrochloric acid. The aim of acid hydrolysis during CNC production is the degradation of amorphous regions and keeping intact crystalline regions. During hydrolysis firstly, polysaccharide bounds on surface of fibrils are eliminated, and then amorphous regions are disintegrated to release crystalline rodlike cellulose [21]. After glucose-chain depolymerization reaches an optimum level, residual of acid and impurities are removed by centrifugation and dialysis processes, and then additional mechanical process is done to obtain uniform nanocrystals [21]. At the end of acid hydrolysis, rodlike rigid CNCs are produced in 3–35-nm diameter dimensions and in 200–500 nm length dimensions [8]. Although, length dimension of CNC can reach micrometers, it remains shorter than CNF [9]. Dimensions of crystals are affected degree of crystallinity of cellulose sources [9, 21]. Apart from degree of crystallinity, reaction conditions as duration, temperature, and concentration of acid influence dimensions of crystals. According the type of acid, it is possible to obtain different surface functionalities. For instance, while HCl causes weakly negatively charges, H_2SO_4 leaves more negatively charges on surface of produced CNC [21].

Although in literature "nanocrystal" and "nanowhisker" cellulose terms could define the same thing, some researches prefer to use nanowhisker terminology in their studies. Therefore, it was aimed to give some examples of hydrogel studies based on specifically nanowhisker cellulose.

Like nanofibril and nanocrytal celluloses, nanowhisker cellulose has been used as a reinforcer agent in polymer-based hydrogel network to enhance mechanical properties of hydrogel. For example, the researches were aimed to enhance mechanical properties of polyvinyl alcohol (PVA)-based hydrogel by surface oxidized microcrystalline cellulose whiskers [22]. Incorporation of MCC whisker into PVA matrix was enabled by direct chemical crosslinking, and they proposed that PVA/MCC whisker hydrogel might be a suitable application for soft tissues in the biomedical field. Also, another group used direct chemical crosslinking method [13]. They crosslinked the cellulose nanowhiskers with poly(methyl vinyl ether-co-maleic acid) (PMVEMA) and poly (ethylene glycol) (PEG). They aimed to find the effect of various concentrations of CNW on polymer matrix. The expected crosslinking mechanism was esterification reaction between hydroxyl groups on the cellulose, terminal hydroxyl groups of PEG, and carboxylic acid groups on the PMVEMA. When they compared water absorption of pure CNW film, CNW incorporated PEG-PMVEMA film, and without CNW PEG-PMVEMA film, results indicated that only CNW/PEG-PMVEMA film showed good swelling and retained integrity performance. They suggested that this is an indication of crosslinking between CNW and polymers. Also, they found that gel content of the films were directly proportional with CNW content.

2.1.2 Cellulose Nanofibrils

It is possible to find nomenclature of this type of cellulose in literature as cellulose nanofibrils (CNF) or nanofibrillated cellulose (NFC).

Cellulose nanofibrils generally are produced by using mechanical forces such as high-pressure homogenizer. Unlike CNC structure, CNF consists of both amorphous and crystalline regions and is more flexible [10]. However, CNF has lower degree of crystallinity than CNC. CNF has on average a 5–50-nm diameter dimension and few micrometer length dimensions [8]. Besides mechanical disintegration, TEMPO oxidation [10] and enzymatic hydrolysis are used to decrease energy demand. CNF has the ability in forming physically entangled networks at low concentrations [10].

To obtain high-quality cellulose fibrils, the combinations of methods are being developed. Some of conventional and nonconventional examples were shown in Fig. 2. The need of desired characteristics of cellulose fibrils sustains to improve processes about production of cellulose fibrils. Around 12 companies are commercially/pre-commercially producing cellulose nanofibrils in global scales. The cost of the method directly affects the commercialization of cellulose nanofibrils. There are still no optimal methods and/or conditions to obtain high-quality and low-cost cellulose nanofibrils.

2.2 Bacterial Cellulose

Bacterial nanocellulose (BNC) is formed by bacteria as pure nm-sized cellulose fibers, and it has no functional groups except hydroxyl groups [7, 21]. Large fiber surface that gives opportunity of strong interactions with surroundings, ability of

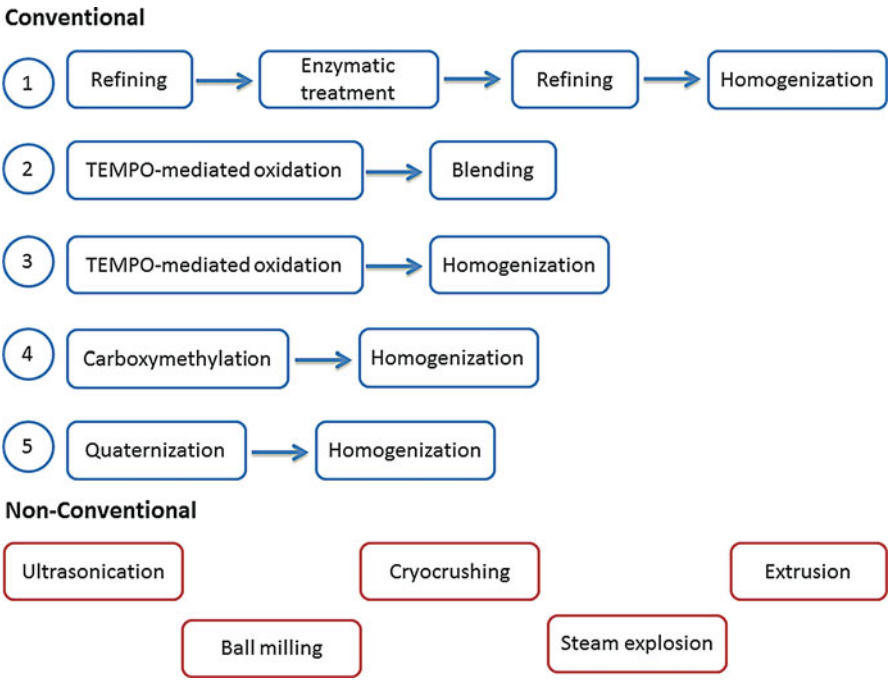

Fig. 2 Conventional and nonconventional methods of cellulose nanofibril methods

incorporation of high amounts of water, well-defined cellulose network structure, high crystallinity, DP, and mechanical strength values can be counted among remarkable features of BNC, in contrast to other nanocelluloses. Also, production of BNC from low molecular weight substrates and control change of cellulose synthesis are other differences from plant-based nanocelluloses [21].

The cellulose fibers produced by bacteria forms ribbons and then specific 3D nanofiber network. This specific 3D structure gives it facility used as template for tissue growth [7, 21].

Unlike shaping from solution which is a single method for cellulose materials from other sources, bacterial cellulose can be shaped in situ during fermentation process with desired shapes [7], such as flat materials which can be produced during static or and BCN in spheres and fibrils shaped under agitated cultivation. Also, thickness and size of bacterial cellulose products can be controlled during cultivation process.

3 Hydrogel

Hydrogel is a three-dimensional hydrophilic network of polymers that can swell with the absorption of water. It has various application fields such as in agriculture industry, biotechnology area, food industry, pharmaceutical area, etc. Hydrogels

can be made from synthetic or natural polymers. The increasing demand for biocompatible, biodegradable, environmentally friendly, and low-cost products led to the replacement of synthetic polymers with natural ones. Among the natural polymers, cellulose is the most attractive one because of its unique properties such as abundance in nature, nontoxicity, and hydroxyl groups on its backbone that give it the opportunity of chemical modifications with different functional materials. Cellulose in the form of native, modified, nanoscale, or even in gel form (e.g., bacterial cellulose) can be used to form hydrogels with numerous aims.

Recent advances in hydrogel-based researches have been depended on reducing limitations and problems caused by less solubility, high crystallinity, non-biodegradability, unfavorable mechanical and thermal properties, unreacted monomers, and toxicity of crosslinking agents [23]. For this reason, most researches have redirected their studies based on biodegradable and renewable sources to produce biocompatible and high-mechanical strength hydrogels. Therefore, cellulose, which is the most abundant polysaccharide polymer in nature, is a favorable polymer due to its unique linear structure, functional groups, and biocompatibility to form hydrogel. In this chapter, the aim is giving brief information about hydrogel formation techniques mostly used for cellulose-based hydrogels, including cellulose structure, properties, cellulose derivatives, nanocrystal cellulose, nanofibril cellulose, nanowhisker cellulose, and bacterial cellulose. Then, hydrogel formation techniques are explained in detail with cellulose-based hydrogel studies.

3.1 Hydrogel Formation

The importance of crosslinks in a hydrogel system is prevention of its dissolution in an aqueous system [24]. Mainly, hydrogels can be separated in two categories based on their owing crosslinking types. The first one is “physical” hydrogels that are commonly in “reversible” formation, and the second type is “chemical” hydrogels that are in “permanent” formation. Due to their covalent bonds to enhance the three-dimensional network, hydrogel formation is not changing in chemical hydrogels. Physical interactions such as ionic, H- bonding, hydrophobic forces, and molecular entanglements between different polymer chains [24] are active in physical hydrogels that result in changing structure. While chemically crosslinked hydrogels can exhibit changes in swelling property due to external conditions such as pH and ion charge of the external medium, physically crosslinked hydrogels can give response to environmental changes by dissolving or swelling [25].

3.1.1 Chemically Crosslinked Hydrogels

Although there can be found several chemical approaches in literature for hydrogel production, basically, preparation of chemically crosslinked hydrogels can be classified in two ways. First one is that polymerization of hydrophilic monomer is achieved with crosslinking agent and second one is crosslinking water-soluble polymers directly [25]. The authors briefly showed (Fig. 3) main differences between abovementioned chemical crosslinking approaches in their studies [25].

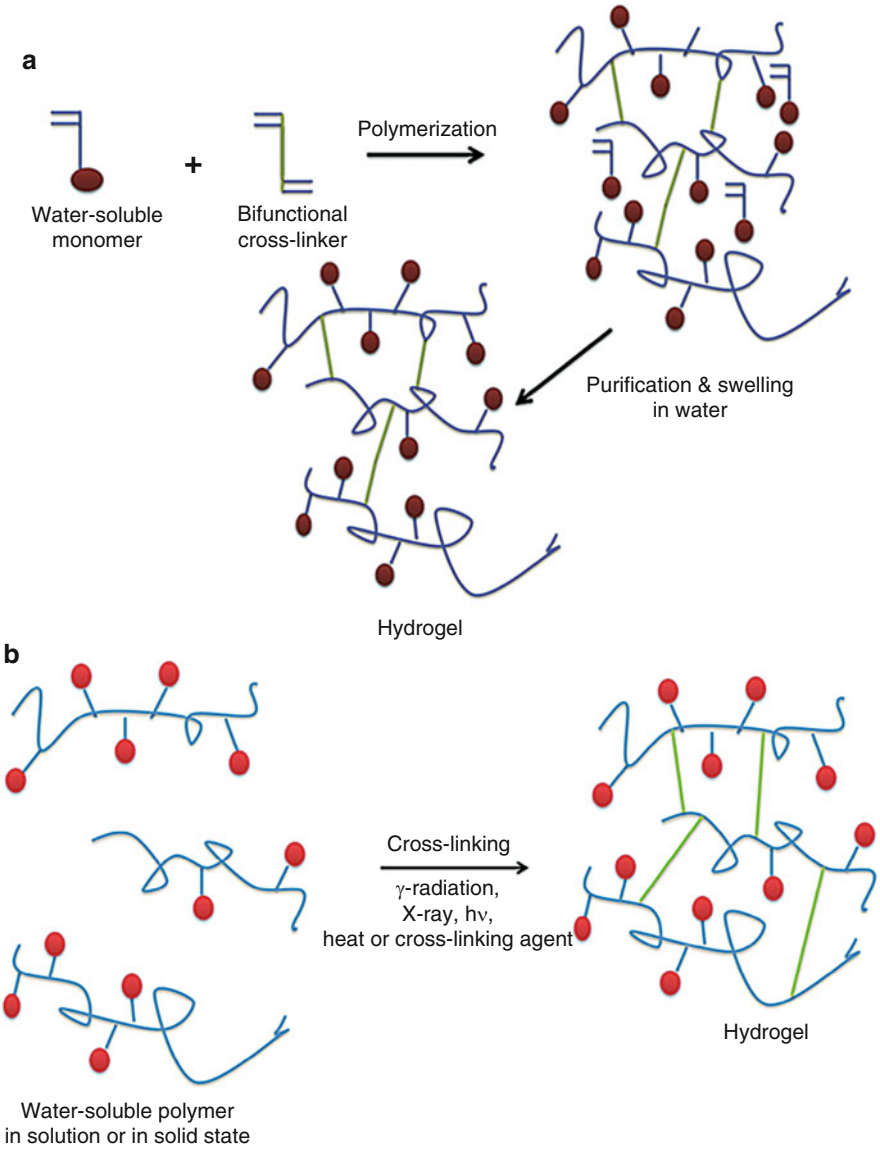

Fig. 3 Basic hydrogel formation mechanisms as (**a**) chemical and (**b**) physical. (Reprinted with permission from [25]. Copyright © 2015, Elsevier)

Poly(acrylic acid), poly(vinyl alcohol), poly(vinyl-pyrrolidone), poly(ethylene glycol), polyacrylamides, and some polysaccharides can be listed in mostly used and nontoxic water-soluble polymers that are used in hydrogel forming [25]. Water solubility of these polymers comes from their functional groups such as OH, COOH, and NH_2 which have an important role in hydrogel formation [24]. Therefore,

functional crosslinking agents react with these chemical reactive groups of water-soluble polymers to form hydrogel [24] via various chemical reactions that will be mentioned below sections. Crosslinking agents can be separated in two classes based on owing reactive groups, esterifying agents consisting of carboxylic acids and carboxylic anhydrides, and etherifying agents consisting of organochlorine, epoxide, and vinyl compounds [26]. In three-dimensional polymerization method, using toxic crosslinking agent causes extra purification steps to remove the residue of these compounds. However, it is possible to produce hydrogels directly by using water-soluble polymers without any purification steps.

Free-radical polymerization is mostly the preferred method for hydrogel preparation due to its high polymerization rate and application capability in aqueous mediums. The main mechanism in this method is polymerization of monomers by the initiators. In cellulose-based applications, cellulose produces free radicals because of initiators, and then interactions between monomers and cellulose occur to produce graft polymers to produce hydrogel [27]. Polymerization can be induced chemically either by free-radical-generating compounds also named "initiator" such as benzoyl peroxide, 2,2-azo-isobutyronitrile (AIBN), ammonium peroxodisulphate (APS) [25], potassium persulfate (KPS), *N*, *N*, *N*′*N*′-tetramethylene-diamine (TEMED) [24], or by physically using UV-, gamma- or electron beam radiation. By radical polymerization method, hydrogel features such as swelling can be adjusted by the amount of crosslinking agents [24].

It is possible to obtain hydrogels by radiation-induced crosslinking in water without using any toxic crosslinking agent under mild conditions. Although radical formed during irradiation might be a limiting factor for biologically active substances [24], this method is favorable in many fields such as pharmaceutical, food, and drug because it is not including toxicity unlike crosslinking agents [26, 28].

During irradiation of aqueous solutions of polymers process, radicals can occur on the polymer chain by homolytic scission of C–H bonds, and due to radiolysis of water molecules, hydroxyl radicals occur. These radicals cause the formation of macroradicals, and macroradicals which exist on different chains lead to formation of covalent bonds, and at the end, crosslinked network structure is formed. Properties of hydrogels that are made by this way can be controlled by adjusting radiation dose and polymer concentration [24].

Strong intermolecular hydrogen bonds of cellulose restrict its solubility in normal aqueous solitons, so development of a hydrogel from only cellulose solution is difficult. Therefore, alkaline or alkaline/urea aqueous solutions are used to form hydrogel from cellulose by using crosslinking agents.

3.1.2 Physically Crosslinked Hydrogels

For production of physically crosslinked hydrogels, instead of crosslinking agents, ionic, H- bonding, hydrophobic connections between different polymer chains develop hydrogel network. These connections can be formed by different mechanisms. For instance, freeze-thawing procedure can be used repetitively to produce microcrystals that cause hydrogel formation. Also, hydrogels can be formed as result of ionic interaction between polyelectrolyte and oppositely charged multivalent ions.

Freeze-thaw method is a hydrogel formation method in which freeze-thawing cycling is repeated more times to cause ice crystals formation due to phase separation of polymer solution, and at the end of the procedure, insoluble gel is obtained. Freeze-thaw or crystallization method is a favorable method due to some of its advantages such as being an energy saver and environmentally friendly because it does not require additional crosslinking agent. Also, it is possible to control the hydrogel mechanical properties by changing parameters of freeze-thaw method such as cycle number, temperature, and time. However, being time-consuming might restrict its usage.

Commonly, cellulose derivatives such as methyl cellulose, carboxymethyl cellulose, hydroxypropyl cellulose, and hydroxypropylmethyl cellulose are preferable in physical crosslinking of cellulose. Because they contain hydrophobic groups, and they have repelling effect to hydroxyl groups of close cellulose chain that prevent intermolecular hydrogen bonding.

Interpenetrating polymer networks (IPNs) are designed to increase mechanical strength and swelling/deswelling response of hydrogels. IPNs are combination of two crosslinked polymers, where one is crosslinked and/or synthesized within other or both are crosslinked at the same time. There is no any covalent bond between two networks. When the two networks are formed at the same time by independent, noninterfering ways, this is called "simultaneous IPN"; if previously formed single network swells in a solution including mixture of monomer, initiator, and activator with or without crosslinker, it is called "sequential IPN." Sequential IPN is separated into two subclasses according to the presence of crosslinker. If crosslinker is present, it is named "fully IPN"; if there is no crosslinker, it is "semi-IPN" [29].

3.2 Production of Cellulose Hydrogels

3.2.1 Solution-Based Prepared Cellulose Hydrogels

The presence of abundant hydroxyl groups of cellulose cause inter- and intramolecular hydrogen bonding networks that give hydrophobicity and restricted dissolution of cellulose in common solvents such as ethanol, methanol, and acetone [30]. Therefore, to produce cellulose hydrogel from native cellulose, dissolution of it must be achieved. The common solvents of cellulose are lithium chloride/dimethylacetamide (LiCl/DMAc), *N*-methylmorpholine-*N*-oxide (NMMO), alkali/urea (or thiourea), and ionic liquids (ILs) [26, 28, 30]. After the dissolution, crosslinking of cellulose chains is accomplished to form a hydrogel [26] physically via ionic interactions, hydrogen bonding, and physical entanglements instead of covalent bonds.

There are various solvent systems that can be used for preparation of cellulose hydrogel. The most common solvent systems are LiCl/dimethylacetamide (DMAc), *N*-methylmorpholine-*N*-oxide (NMMO), and alkali/urea.

LiCl/DMAc solvent system is based on breaking of intermolecular hydrogen bonding from hydroxyl groups of cellulose at C6 position. Li^+ cations have ionic interaction with free DMAc molecules, while Cl^- anions make hydrogen bonding with hydroxyl groups. Hence, cellulose polymers are homogenously dispersed in

LiCl/DMAc solvent system [31] NMMO solvent system is still used in commercial production of regenerated cellulose. The amount of water is important in this solution system. NMMO molecules move freely at 100 °C that result in replacement of water molecules closed by cellulose. At elevated temperatures, around 150 °C, crystal structure is completely destroyed, and transparent cellulose solution is obtained [32]. Isourea or thiourea with sodium hydroxide is commonly used for alkali/urea solution to dissolve cellulose. Different amount ratios of NaOH and urea complexes showed different characteristics of cellulose hydrogel. In addition to that, temperature also effect the gelation result mainly elongation and toughness.

3.2.2 Bacterial Cellulose-Based Hydrogels

Bacterial cellulose (BC) is synthesized by some nonpathogenic bacterial strains as *Acetobacter*, *Komagataeibacter*, and *Gluconacetobacter* in the gel form. High tensile strength, high modulus, high water absorption capacity, highly biocompatibility, high crystallinity, and high purity are promising properties of bacterial cellulose for hydrogel applications [28].

The advantage of bacterial cellulose does not require additional purification procedure unlike cellulose obtained from nature including lignin and hemicellulose and does not require crosslinking agent [26].

Besides plant-based cellulose nanofibrils, the researches [20] produced cellulose nanofibers from bacterial cellulose in the 10- to 90-nm width and 1–10-μ length by acid hydrolysis treatment. Then they produced a hydrogel network composed of polyvinyl alcohol and bacterial cellulose-based CNF with the crosslinking of glutaraldehyde. Obtained hydrogel showed three-dimensional interpenetrating polymer network with the well-dispersed bacterial cellulose nanofibers and pores with the size in several to dozen microns. CNF including hydrogel showed improved mechanical characteristics with the rise of tensile strength and improved thermal stability by shifting decomposition temperature to higher temperature.

3.3 Cellulose Derivative-Based Hydrogels

As mentioned above, cellulose is non-soluble in water due to extended hydrogen bonds on its structure. On the other hand, hydroxyl groups of cellulose make it suitable for chemical modifications with methyl and ethyl units to obtain water-soluble cellulose derivatives such as methyl cellulose (MC), carboxymethyl cellulose (CMC), ethyl cellulose (EC), hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), and hydroxypropylmethyl cellulose (HPMC) (Fig. 4). Modified cellulose-based hydrogels can be formed either by chemical crosslinking or physical crosslinking.

3.3.1 Chemical Crosslinking

Hydrogels formed by covalent bonds in the presence of crosslink agents are irreversible and have more stable structure than physically formed one. The disadvantage of chemically formed hydrogels might be the effect of unbounded groups of

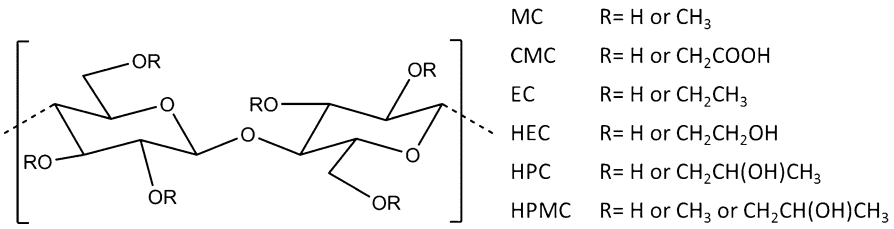

Fig. 4 The chemical structures of cellulose derivatives

crosslink agents that might cause undesirable binding in biological systems. They can be classified based on the chemical reaction involved in crosslinking.

Esterification occurs in hydroxyl and carboxyl groups of cellulose (or its derivatives) and other polymers such as polysaccharides or synthetic polymers, respectively. Requirements of esterification are high temperature and a crosslinker agent. 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC), citric acid, and fumaric acid are commonly used in an esterification reaction to form a hydrogel. EDC promotes crosslinking between carboxyl groups and hydroxyl or amine groups with the formation of nontoxic, water-soluble urea derivative [26, 28]. EDC is preferable for crosslinking reaction because of high conversion efficiency, mild reaction conditions, nontoxicity, and easiy separation by products and compatibility with materials. Also, during the esterification of cellulose and citric acid, anhydride intermediate is formed [28].

Michael-type addition reaction occurs between hydroxyl groups of cellulose and carbon-carbon bonds. Divinylsulfone (DVS) is used as crosslink agents, but its toxicity restricts its usage [28].

Epoxide crosslinking occurs between epoxy groups of compound and hydroxyl groups of cellulose. Diepoxy compounds such as ethylene glycol diglycidyether (EGDE) which is less toxic and poly ethylene glycol diglycidyl ether (PEGDE) are some examples of epoxide crosslinkers. Epoxide reaction requires strong basic conditions at around pH 11 and high temperature as 60 °C. Alkyl halide reaction happens between halide functional groups and hydroxyl groups of cellulose in strong alkaline conditions. Also, epichlorohydrin is a crosslinker with both halide and epoxide functional groups [30].

Free-radical copolymerization can be achieved with gamma irradiation initiation which is a clean method because there is no need for initiator agent, but its applicability is narrow due to sources [30]. UV initiation, electron beam (EB) [28], or chemical initiation using potassium persulfate (KPS) or ammonium persulfate (APS) by free-radical compounds can be used as an alternative to gamma radiation. *N*, *N*-methylene bisacrylamide (MBA), diallytartardiamide (DATDA), DVS, and PEGDE are some crosslinkers used in free-radical copolymerization [30].

3.3.2 Physical Crosslinking

Physical crosslinking can be achieved via hydrogen bonding, hydrophobic interactions, ionic interactions, and chain entanglements to form cellulose hydrogels.

Unlike chemically formed hydrogels, physically formed hydrogels do not require a chemical agent that can result in toxic by-products to crosslink polymer chains, and this gives the opportunity for application in food and pharmaceutical areas. However, the reversible structure of hydrogels made by physical interactions limits its utilization.

3.4 Cellulose Nanofibril (CNF) Hydrogel

Introducing micro-sized or nano-sized particles in three-dimensional network of hydrogel is a new application area to produce hydrogels with enhanced existing properties such as mechanical strength, swelling, and absorption. It is difficult to exhibit high swelling ability and high mechanical properties at the same time in conventional hydrogel networks [33, 34]. Besides low mechanical strength, conventional hydrogels exhibit lack of low-breaking strain and sensitivity toward fracture when handled at swollen state [16].

For this purpose, nanoparticles with hydrophilic properties have been tried to introduce the hydrogel structure and enhance its properties. Among these materials, synthetic nanoparticles such as clays of montmorillonite, bentonite, kaolinite, and sepiolite can be listed [34]. However, dispersion problems of inorganic clays might be a limited factor for use in hydrogel systems [16, 34] because there might be need of an extra processing step such as modification or special mixing of clays [16].

Some characteristics of nanocellulose make it advantageous and differ it from synthetic nanoparticles such as being renewable and lightweight with a density 1.5 g cm^{-3}, low-cost, safe processing conditions [35], strong reinforcing effect, high-aspect ratio, biodegradability, sustainability [16] and, self-assembly behavior [36].

Cellulose nanofibrils (CNFs) which are flexible elongated nanoparticles possesses large surface-to-volume ratio due to their nanometer diameter that facilitates dissipation of energy into the composites including CNFs by interfacial interactions. Dispersed CNFs can readily form networks in aqueous media, and they are better than nanocrystals to increase viscosity of a hydrogel because of entanglement provided by fibers [36]. Dispersion mechanism of CNF differs based on the presence of any chemical pretreatment before disintegration to nanofibrils. Without the chemical pretreatment, dispersion is achieved by entanglement in water. On the other hand, chemically treated CNF aligned spontaneously, and dispersion is performed by the repulsive forces as in the case of carboxylate CNF [18]. There is capability of CNFs to form hydrogel at even low concentrations, and stability of these hydrogels is provided by transient interactions such as entanglement of fibrils, nonspecific ionic interactions, and hydrogen bonds which are sensitive to environmental changes such as chemical or physical [17]. High stiffness and modulus properties of nanocellulose fibrils make them promising reinforcing fillers to improve existing hydrogel properties. Apart from high stiffness and modulus properties, ability of formation continues; network makes both cellulose nanocrsytals and nanofibrils a reinforcer agent in a polymer matrix [16]. Reinforcement of

nanofibers is achieved with complete dispersion of particles in hydrogel matrix due to increased contact surface area between hydrogel chains and fiber structures [33].

The scientists in their research pointed out reinforcing ability of cellulose nanofibrils produced from softwood kraft pulp in composite hydrogel which was produced by free-radical polymerization of monomer of acrylamide (AAm) at the presence of 10 wt.% CNF, potassium persulfate as initiator, and *N*, *N*′-methylenebis (acrylamide) (MBA) as crosslinker [37]. In this composite hydrogel, while the covalent bonds were produced in PAAm matrix, dynamic hydrogen bonds were produced between CNF and matrix. During hydrogel formation interaction between hydroxyl groups of CNF and PAAm matrix with hydrogen bonds caused adsorption of polymer chains onto CNF surface to show reinforcing capability at the interface. According the research results [37], dynamic hydrogen bonds between the matrix and CNF improve the mechanical properties via enhancing fracture resistance, self-recovery, and energy dissipation.

In another study [16], CNF was introduced to the poly(acrylic acid-co-acrylamide) matrix which was produced by free-radical polymerization in the presence of bisacrylamide as crosslinking agent (Fig. 5). Grafting of polymers chains onto the CNF was achieved by transfer reaction between sulfate anion radicals and hydroxyl groups of CNF. In this study, the effect of CNF on the swelling and mechanical performance of the hydrogel was examined. Results showed that increasing CNF content led to reduction of swelling ability of hydrogel, and they ascribed this situation to entangled cellulose fibrils and chemical grafting of polymer chains that increased crosslinking density of the hydrogel. Unlike swelling behavior, CNF caused the improvement of modulus and compression strength, and this attributed to good dispersion of CNF and grafting polymer chains onto CNF.

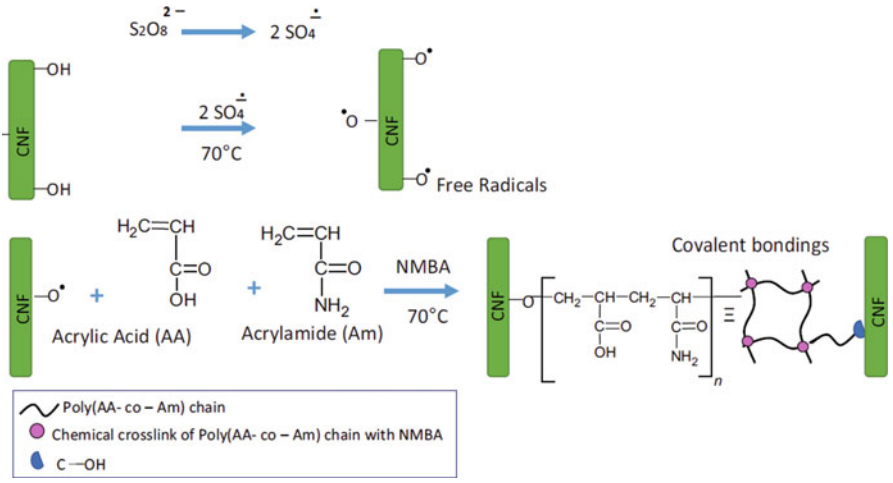

Fig. 5 Free-radical polymerization reaction on cellulose and acrylic acid. (Reprinted with permission from [16]. Copyright © 2016, Springer)

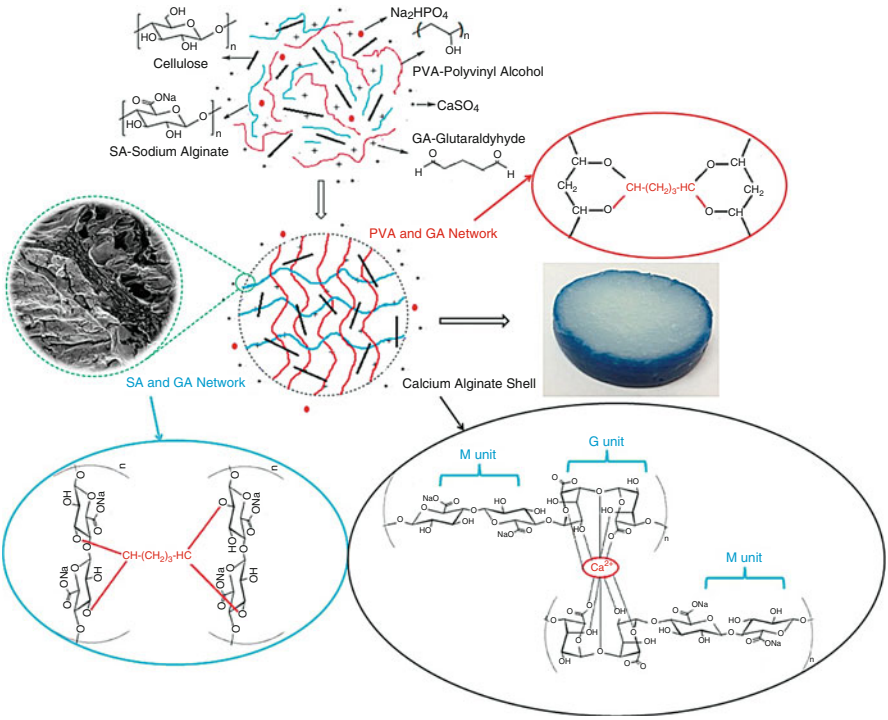

Fig. 6 Schematic representation of core shell structure. (Reprinted with permission from [38]. Copyright © 2016, Elsevier)

Also, a polyacrylamide-methylcellulose (PAAm-MC) hydrogel by free-radical polymerization technique was performed and then incorporated cellulose micro- and nanofibers into hydrogel matrix to test reinforcement effect of cellulose particles [33]. The results exhibited that while the mechanical properties of hydrogel increased with the addition of micro- or nanofiber cellulose, they caused small pore-sized hydrogel structure.

Differently from above studies, a research group introduced CNF in a hydrogel system which was produced by two distinct methods for adsorption and desorption dye studies [38]. This hydrogel system consisted of two parts as core and shell which were produced by IPN and semi-IPN networks systems, respectively (Fig. 6). Polymer matrix was produced from sodium alginate (SA), polyvinyl alcohol (PVA) with Ca^{+2}, and glutaraldehyde, and then CNF was incorporated the hydrogel.

Besides the native cellulose nanofibers, nanofibers of cellulose derivatives or modifications can be utilized in the formation of cellulose nanofiber-based hydrogel. TEMPO oxidation is the most preferred method to obtain cellulose with carboxyl groups. The study showed cellulose anionic hydrogel preparation from TEMPO-oxidized cellulose nanofibers [39]. For this study, TEMPO-oxidized CNF was dissolved in NaOH/urea aqueous solution, and then the three-dimensional structure

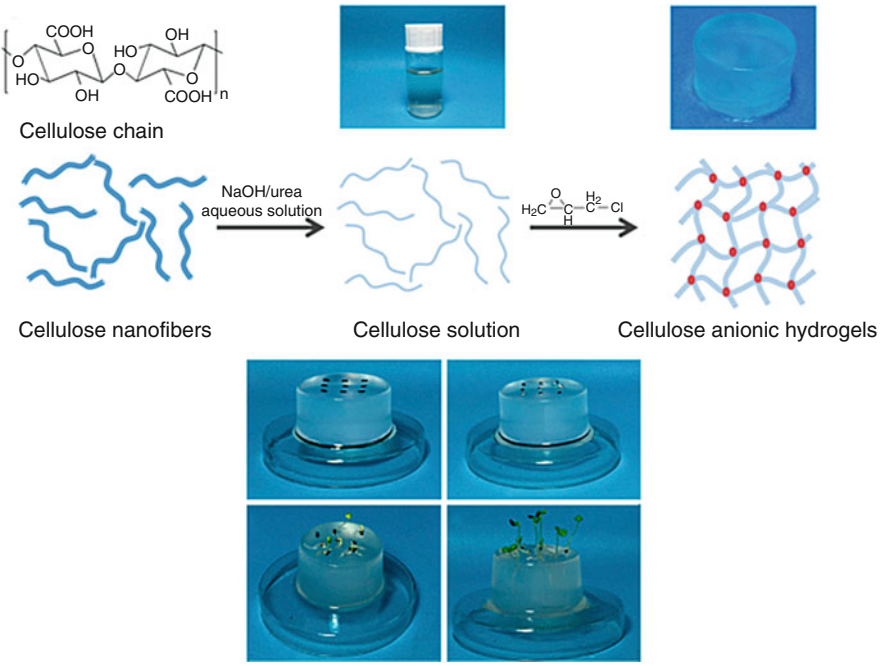

Fig. 7 Preparation of TEMPO-oxidized cellulose hydrogel and growing of sesame seeds by days. (Reprinted with permission from [39]. Copyright © 2017, ACS Publications)

of the hydrogel was maintained by using epichlorohydrin (ECH) as a crosslinker. Unlike the utilization of CNF for improvement of mechanical properties of hydrogel, the researches aimed to make a hydrogel with a carboxylate content to test for seed germination and growth [39]. Therefore, the main reason was the test of the water absorption of the hydrogel. The results showed that water absorption was directly proportional to carboxylate content of the hydrogel, because as the carboxylate content increases, the hydrophilicity increases and causes more water absorption and enlargement of the pore sizes (Fig. 7).

Another study benefited from surface carboxylation of CNF by TEMPO oxidation [18]. However, in this study and unlike other studies, a crosslinker agent was not used, hydrogel formation was provided by partially assemble of carboxylate CNF, and there was a dilute acid addition (pH 2) under the pKa (3–4) of the carboxyl groups. Also, some researchers examined reinforcement ability of carboxylated CNF in gelatin hydrogel network, and they suggested that the reinforcing ability of CNF was due to its intrinsic stiff characteristic [19]. In other study, hydrogel was produced from refined bleached beech pulp (RBP) by UV polymerization of *N*-vinyl-2-pyrrolidone with Tween 20 trimethacrylate as crosslinker and reinforced this hydrogel with carboxymethylated, nanofibrillated cellulose (c-NFC) [40]. According the results, it was suggested that hydrogel properties such as swelling behavior and compression moduli might be controlled with the amount of c-NFC and its degree of

substitution. Because the results revealed that higher amount of c-NFC caused decrease in swelling ratio but increase in compressive moduli. Additionally, high DS of c-NFC increased the swelling ratio of hydrogel.

Apart from carboxyl groups, also aldehyde groups can be introduced onto surface of CNF. A hydrogel network was produced from CNF which was modified with TEMPO-mediated oxidation procedure to introduce aldehyde groups on CNF surface [17]. Crosslinking was performed by amine-aldehyde reaction and ionic interactions. To achieve crosslinking by amine-aldehyde reaction, diamines which were ethylenediamine (EDH) and hexamethylene diamine (HMDA) were used as crosslinkers. It tried to show the effect of crosslinker molecule and concentration on elastic modulus of CNF based hydrogel. Results showed that without crosslinker water absorption increased, but with the highest degree of Young's modulus (highest degree of crosslinking), water absorption reduced. It might be said that these results are similar with result of [16] where crosslinking density caused reduction in swelling behavior.

Until here we mentioned from reinforcement studies of CNF, but some studies benefited hydrogel formation capability of CNF to produce stimuli-responsive hydrogels. For instance, smart hydrogels were produced from carboxylated CNF to sense, AgNPs, laccase enzyme and, 2,4,5-trichlorophenol TCP, respectively [41–43].

3.5 Cellulose Nanocrystal (CNC) Hydrogel

Biomedical and tissue engineering fields frequently benefited from different hydrogel applications to improve biodegradable, nontoxic, environmentally friendly hydrogel networks. Injectable hydrogel is one of the new hydrogel applications, and there is no need for gelation initiators such as heat, UV, and chemical agents to make it favorable for biomedicine applications. Injectable hydrogels can be prepared in situ and applied by extruding hydrogel components from a syringe to the target location in vivo. Besides these advantages of injectable hydrogel, its low mechanical strength is one limited factor for its usage. Therefore, reinforcement of this hydrogel type by biodegradable, nontoxic agents is an important point for in vivo applications. Some scientists have been using cellulose nanocrystals (CNC) in their injectable hydrogel studies to enhance mechanical properties of hydrogels [44, 45]. Carboxymethyl cellulose and dextran-based hydrogel were prepared and reinforced with CNCs and aldehyde-functionalized CNCs (CHO-CNCs) [44]. Aldehyde-functionalized CNC and aldehyde-functionalized dextran were mixed, and mixture was coextruded with hydrazide modified CMC. It was suggested that unmodified CNC acted as filler and modified CNC as chemical crosslinker. CNC-reinforced hydrogels were formed by hydrazone crosslinks. Both CNC and CHO-CNC showed well dispersion in hydrogel, and injectable hydrogel reinforced with CNC showed more elastic but less swelling behavior compared to unfilled gels. Additionally, CNC reinforced poly(oligoethylene glycol methacrylate) (POEGMA) injectable hydrogel was obtained by the same way [45]. In here, covalent hydrazone crosslinks between POEGMA precursors and physical crosslinks between CNC and POEGMA were

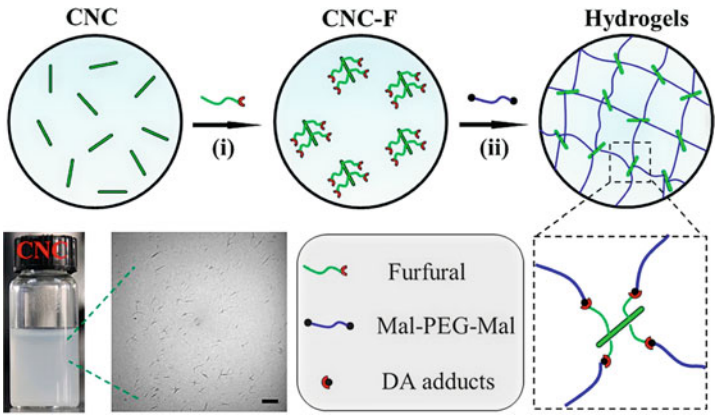

Fig. 8 Preparation of self-healing CNC hydrogel. (Reprinted with permission from [46]. Copyright © 2017, ACS Publications)

formed to maintain the hydrogel structure. The researchers suggested that the incorporation of well-dispersed CNC decreased gelation time and swelling and increased the degradation time and enhanced the mechanical performance.

Also, the Diels-Alder (DA) click reaction was performed to produce a self-healing hydrogel from the furfural modified CNC (CNC-F) and poly(ethylene glycol) with maleimide terminal groups (MAL-PEG-MAL) [46]. While PEG served as backbone, CNC acted as both reinforcer and chemical crosslinker (Fig. 8). It was explained that the reasons of choosing DA reaction in this study were high efficiency, high selectivity, and high yields without by-products and no need for extra chemical reagents. During the thermally induced DA reaction, covalent crosslinks were established between furyl groups and maleimide groups. It was obtained that self-healing hydrogels had excellent recovery ability and good mechanical characteristics which were adjustable by substitution degree of furyl functional groups and the mole ratio furyl to maleimide.

Apart from using CNC as reinforcer agent to strengthen mechanical performance of hydrogel, there are some studies which benefited CNC in various fields such as drug release studies, stimuli-responsive hydrogel, or absorption studies. A hydrogel system was produced from cationic cellulose nanocrystals (CNC) and anionic alginate for drug delivery [47]. Surface cationization of CNCs was achieved by chemical modification with 2,3, epoxypropyl trimethylammonium chloride and physical adsorption of polyethylenimine (Fig. 9). Hydrogel formation was performed by a double-membrane hydrogel system in which combination of anionic alginate and cationic CNC was provided by electrostatic interactions and ionic crosslinking. While the inner part of hydrogel system composed of cationic CNC and anionic alginate, the outer part composed of alginate. Syringe-like device can be used to adjust the shape and size of inner hydrogel part; the duration time can regulate outer part thickness. The results revealed that doubl-membrane hydrogel structure and drug release behavior are suitable for biomedicine applications.

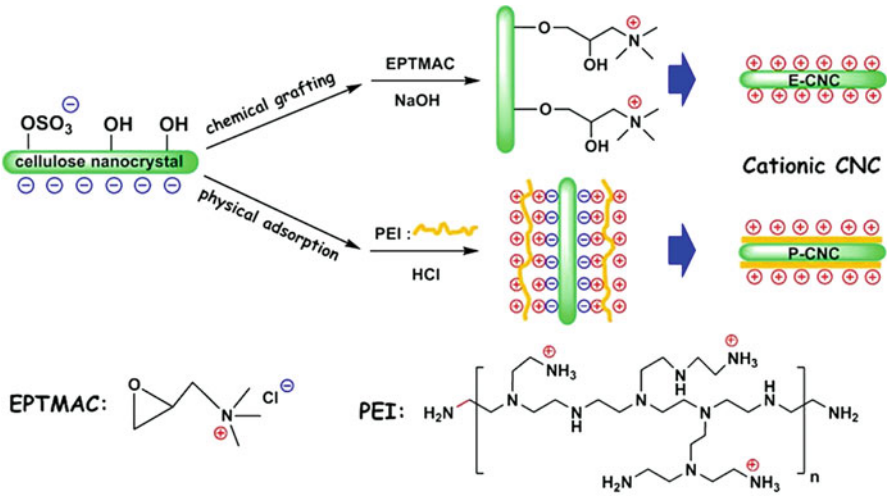

Fig. 9 Synthesis pathways of cationic CNC with the chemical grafting and physical adsorption strategies. (Reprinted with permission from [47]. Copyright © 2016, ACS Publications)

4 Special Cellulose Hydrogel

4.1 Stimuli-Responsive Hydrogels

Stimuli-responsive or smart hydrogels are designed to change their characteristics such as network structure, mechanical strength, and permeability according the environmental alterations. These environmental stimuli might be chemical such as pH, ion charge, chemical compounds, or physical stimuli including temperature, light, electric field, magnetic field, or pressure. The two conditions, temperature and pH, have physiological significance; hence, their responsive hydrogels have been widely studied.

Thermo-sensitive hydrogels are classified into two sections as positive and negative thermo-reversible systems. Polymer solutions have two distinct temperature values which are upper critical solution temperature (UCST) and lower critical solution temperature (LCST) in which polymer solution shrink or contract by below UCST or above LCST, respectively, in positive thermo-responsive systems. The negative thermo-responsive hydrogels are generally be liquid at room temperatures and become gel above 30 °C.

The most used materials for gel preparation are acrylic acid copolymers and *N*-isopropylacrylamide derivatives where they swell below LCST and shrink above LCST in water.

Cellulose derivatives are preferable in preparation of stimuli-responsive hydrogel. Cellulose derivatives are generally water soluble, and hence, it can be gelation with monomers that polymerized during hydrogel preparation. Carboxymethyl cellulose (CMC) is one of the cellulose derivatives [48] and is a fundamental

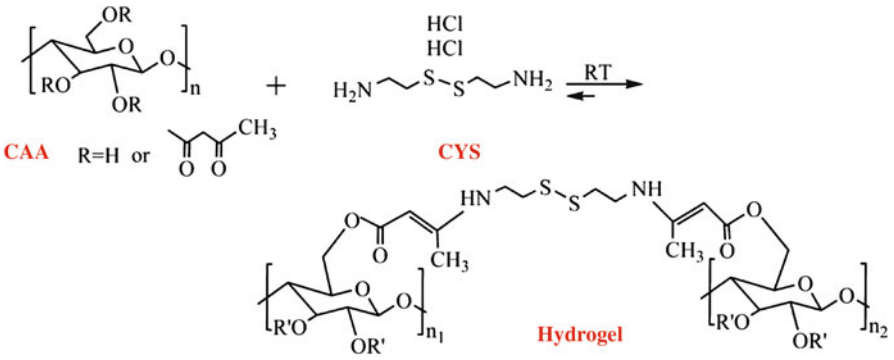

Fig. 10 Redox/pH dual-stimuli-responsive hydrogel by cellulose acetoacetate (CAA) and cystamine dihydrochloride (CYS). (Reprinted with permission from [50]. Copyright © 2017, Elsevier)

material for hydrogel preparation. In addition to this, oxidized CMC was also used in hydrogel with 3,3′-dithiobis propionohydrazide [49]. In addition to this, preparation of hydrogel with cellulose acetoacetate and cystamine dihydrochloride showed redox/pH dual-stimuli responsive (Fig. 10). Enamine and disulfide groups are stimulated by pH and redox, respectively.

Responsive photonic cellulose hydrogels are recently popular in sensor technologies. Photonic hydrogel was prepared by using cellulose nanocrystal, acrylamide, and 2,2-diethoxyacetophenone [51]; a hydrogel was prepared for separation industry [52]. Cellulose nanocrystal, poly(oligoethylene glycol) methacrylate, and poly (methacrylic acid) were used for destabilizing of Pickering emulsions [52]. Bacterial cellulose is also used in pH-responsive hydrogels. The scientists prepared bacterial cellulose-g-poly(acrylic acid-co-acrylamide) hydrogels using potassium persulfate in NaOH/urea solution via bulk polymerization [53]. At neutral pH, swelling ratio increased 30-fold higher than acidic pH [53]. In another study with bacterial cellulose, it mixed with sodium alginate to prepare pH and electric field stimuli-responsive hydrogel [54]. A thermo-responsive hydrogel formation was studied by TEMPO-oxidized bacterial cellulose and elastin-like poly-peptide (ELP). In this hydrogel system, positively charged ELP behaved like a crosslinker for negatively charged nanofibril of bacterial cellulose and formation induced with the temperature rise.

Besides producing directly mechanically reinforced hydrogel, a group [11] benefited from reinforcer properties of cellulose nanowhiskers to produce a smart hydrogel which was thermally responsive. For this purpose, a semi-interpenetrating network of cellulose nanowhisker obtained after sulfuric acid hydrolysis treatment by cotton and *N*-isopropylacyrlamide (NIPAm) was formed by free-radical polymerization in the presence of metyhlenebis acrylamide (MBA) as crosslinker and potassium persulfate (KPS) as iniator. In this study PNIPAm was used as smart material with thermo-responsive feature and CNW as reinforcement material. According their results, a homogenous hydrogel with well-proportioned network structure, dense architecture, and with evenly distributed pores was obtained. Also,

equilibrium swelling ratio (ESR) was enhanced with the incorporation of CNW into the PNIPAm structure. Additionally, other group [14] tried to enhance thermal properties of CNW-reinforced gelatin hydrogel besides mechanical properties. Chemical crosslinking was formed between aldehyde groups of periodate oxidized CNW and free ε- amino groups of the lysine hydroxylysine residues of gelatin. Periodate oxidation causes cleavage at the C2–C3 glycol bond which results to dialdehyde groups at the respective carbon atoms. Therefore, these aldehyde groups act as crosslinker by reacting free amine groups of gelatin. Because as commonly known, gelation is not usable at the higher temperatures (above 35 °C), so they aimed to improve thermal properties of gelatin. Results pointed out that as aldehyde groups increased, degree of crosslinking increased. With the rise of the degree of crosslinking mechanical and thermal properties of gelatin, hydrogel improved but caused the reduction in water uptake ability.

Because of their changing formation by thermal and ionic strength, stimuli-responsive hydrogels are generally preferred in drug delivery and process-based systems.

4.2 Superabsorbent Hydrogels

Superabsorbent hydrogels have the ability retain huge amounts of water or aqueous solutions compared with general absorbing materials [11, 55]. Existent superabsorbent products are usually based on petroleum polymers so production of superabsorbent from natural, biodegradable polymers attracts attention.

Superabsorbent hydrogels have the capability to absorb, swell, and retain aqueous solutions up to hundreds of times their own weight [27]. The unique properties that differ superabsorbent hydrogels from common hydrogels are fast-swelling rate and absorption of extraordinary amounts of water than common ones. It is possible to prepare several hundred microns diameter pore sizes in hydrogel matrix to enhance water movement in the matrix [56]. Most superabsorbents are produced from synthetic polymers such as acrylic acid, sodium, potassium salts of acrylic acid, and acrylamide due to their low cost and high efficiency. Although it is possible to produce economical superabsorbent hydrogels from these synthetic materials, biodegradability and biocompatibility problems of these synthetic materials lead to the looking new materials [27].

As in the conventional hydrogels, using renewable, nontoxic, biodegradable, biocompatible, low cost materials in superabsorbent hydrogels is an emerging application to replace synthetic polymers and reduce negative effects coming from synthetic polymers. Abundance of cellulose and its intrinsic degradability make cellulose a promising material for superabsorbent hydrogel applications. Also, high absorbency, high strength, and good salt resistance features of cellulose-based superabsorbent hydrogels give various applications opportunity. There are several application fields of cellulose-based superabsorbent hydrogels such as in agriculture, personal health care, water treatment, and biomedical field. Some researchers have been tried to produce cellulose-based superabsorbent hydrogel with various properties such as high water absorption performance or stimuli responsive with the alteration in environmental conditions such as pH, salt, or temperature to import

obtained hydrogel systems abovementioned or distinct fields [27]. For instance, it was aimed to produce superabsorbent hydrogel from starch-g-poly (sodium acrylate) matrix with cellulose nanowhisker with pH and salt-responsive behavior [56]. Additionally, a superabsorbent hydrogel based on acrylic acid, acrylamide and 2-acrylamido-2-methyl-propanosulfonic acid, and sodium carboxymethyl cellulose was prepared to test the water absorption ability in aqueous mediums with different salt and pH conditions [57]. Also, a carboxymethyl cellulose and clay-based superabsorbent hydrogel were produced with the purpose of elimination of toxic dyes from water [58]. It was tested cellulose clay-based superabsorbent hydrogel by using methylene blue dye, and results demonstrated that formed hydrogel is suitable for dye decontamination treatments. Additionally, a superabsorbent hydrogel from quaternized cellulose (QC) and native cellulose was produced to improve the biocompatibility, mechanical strength, and antimicrobial activity of disposable diapers [59]. A cellulose and carboxymethyl cellulose-based superabsorbent hydrogel was produced to test its swelling; salt sensitivity and protein release studies were conducted to show it as a candidate hydrogel system in biomedical field [55].

5 Characterization Methods of Cellulose Hydrogels

Characterization assays should be performed efficiently, because the properties of cellulose (and its derivatives) and hydrogels have to be well understood. Depending on their properties, they can be used in usage area effectively. Different kinds of characterization assays for understanding the structure of cellulose hydrogels are summarized in Table 2.

Table 2 Characterization methods and their aims for cellulose hydrogels

Investigation site	Assays	Advantages/disadvantages
Chemical composition	Fourier transformation infrared spectroscopy (FTIR)	+ Easy perform + Trusted result − Sample should be well-dried − Difficult to understand the result
Fibril structure	X-ray diffraction (XRD)	+ Trusted result for fibers − Sample should be well-dried
Fibril strength	Tensile assays	+ Trusted result + Suitable for dry and wet state of hydrogel
General property of hydrogel	Thermal gravimetric analysis (TGA) Differential scanning calorimetry (DSC)	+ Suitable for thermal decomposition and water-retention analyses
Surface property	Scanning electron microscopy (SEM)	− Sample should be well-dried
Fiber size/ property	Transmission electron microscopy (TEM)	− Sample should be well-dried +/− TEM should be performed in low voltage

After preparation of different type of celluloses, they can be easily characterized. Because cellulose can be prepared in dry state that is needed in all characterization assays. However, after it is formed as hydrogel, it should be dried for characterization assays. During the drying process, cellulose fibers are composted, and surface characteristic as ionic strength are changing. Therefore, even some of the characterization assays are not suitable for hydrogel analysis; there are no alternative assays up to now. In this perspective, tensile assays are only assays for analyzing hydrogel correctly.

5.1 Keynotes of Experiments

Fourier transform infrared (FTIR) spectroscopy: FTIR spectrum of the hydrogel should be recorded by Fourier transform infrared spectrophotometer in the range from 400 to 4000 cm^{-1}. If cellulose material is not derived, there is no need to use potassium bromide disk; otherwise the transparent disk should prepared by grinding around 2 mg of the samples 45 mg of KBr and pressing it at high pressure.

Scanning electron microscopy (SEM): After the cellulose hydrogel is completely dried, film is placed on glass plate. If it is possible, surface and cross-section images should be taken. The magnitude can be arranged around 10–100 KX.

Transmission electron microscopy (TEM): Cellulose hydrogel should be dried at ambient temperature. The voltage of electron microscopy is essential that should be around 3–30 kV. Cellulose may be burned at elevated voltages.

X-ray diffraction (XRD): Crystallinity value is important for preparation of cellulose derivatives and hydrogels. Because calculation of crystallinity is based on the pattern of X-ray diffraction, sample surface has to be prepared in smooth.

Thermal gravimetric analysis (TGA) and differential scanning calorimetry (DSC): Both systems use elevated temperatures. The change of weight and heat generation are followed in TGA and DSC assays, respectively. Before analysis, samples should be dried at ambient temperature. Heating rate can be adjusted to 10–20 °C/min for both assays under nitrogen atmosphere.

Tensile sssays: Sample is both prepared in dry and wet states. The difference between dry and wet hydrogel is important which directly affect the usage areas. To increase the reliability of the data, sample should be cut and measured precisely. The calculation of tensile properties such as tensile at break, elongation, and Young's modulus depends on the sizes of hydrogel.

6 Conclusion

Cellulose is the most abundant biopolymer, and because of its binding system, it has found the chance to be used in various areas. However, to increase the quality of material, cellulose is to be prepared in different forms and derivatives. The most used formations and derivatives of cellulose are cellulose nanocrystal and nanofiber and carboxymethyl, methyl, hydroxypropyl celluloses, respectively. Even though there are various studies about preparation of cellulose hydrogels, there is still no

optimized preparation and hydrogel for usage areas. Researchers have continuously found novel hydrogels, but almost each hydrogel has one or more disadvantages such as cost, difficulty of preparation, and restricted usage conditions. With the increasing interest on biomedical area and its products, hydrogels are promising materials for industrial areas.

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Modification of Cellulose

15

Sajjad Keshipour and Ali Maleki

Contents

Abstract

With increasing concerns about synthetic polymers for the environment, the application of natural polymers, especially cellulose due to abundance, biodegradability, nontoxicity, and high functionality, is increasing. For inducing the

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desired properties of cellulose, it's necessary to manipulate the cellulose structure. Therefore, the modification of cellulose becomes important. The modification of cellulose is introducing organic and inorganic compounds on the polymer. A significant variation in the cellulose properties can be observed with the binding of polymers. Also, mineralization of cellulose has attracted a great deal of attention in recent years. This chapter investigated all of these modifications on cellulose.

Keywords
Cellulose · Modification · Cellulose composites · Cellulose nanocomposites · Mineralization of cellulose

1 Modification of Cellulose with Organic and Inorganic Materials

Cellulose is a carbohydrate polymer constructed from the repeating of ß-D-glucopyranose units. The polymer is in nature in different forms and has always been a part of nature and human life, such as wood, paper, or cotton fabrics. Cellulose has a high degree of functionality because of the presence of many hydroxyl groups in this molecule. This most abundant natural biopolymer has characteristic properties such as hydrophilicity, chirality, biodegradability, and high functionality. It has applications in composite materials, textiles, drug delivery systems, and personal care products. In recent years, much attention has been paid to cellulose and its derivatives due to their biological, chemical, as well as mechanical properties. Cellulose and its derivatives can be used as supports due to their renewable, biodegradable, and nontoxic properties. One of the drawbacks of this compound is related to its polar and hydrophilic nature. Surface modification has been used for fixing this problem. The surface structure of cellulose contains highly active and attractive hydroxyl groups toward various chemical modifications with the polymers and inorganic or hybrid organic/inorganic compounds.

1.1 Cellulose Esters

Esterifications with inorganic and organic acids are interesting reactions of cellulose with broad applications in the industry. Cellulose acetate, cellulose nitrate, and cellulose xanthogenate are known as the important esters of cellulose. The cellulose esters were investigated in two main categories including organic and inorganic esters of cellulose.

1.1.1 Organic Esters of Cellulose

The reaction of cellulose with carboxylic acids gives cellulose organic esters with removal of a H_2O molecule. Cellulose acetate is the most important ester of cellulose with industrial applications such as in the sunglasses, linings, blouses, dresses, wedding and party attire, home furnishings, draperies, upholstery, and slip covers.

Cellulose Acetate

The first organic ester of cellulose was synthesized from the reaction of cotton cellulose with acetic anhydride in a sealed tube at 180 °C by Schutzenberger (1865 and 1869) [1, 2]. Franchimont (1879) performed the reaction with H_2SO_4 and $HClO_4$ catalysts as the industrial approach for the production of cellulose acetate [3]. Commercial cellulose acetates have high strength and high melting point and exhibit a high UV stability and film transparency, combined with low inflammability. Acetic anhydride is predominantly implied as the esterification reagent of cellulose, mostly as a liquid, in special cases, also in the vapor phase. High degree of acetylation was reported for bacterial cellulose in 1-*N*-butyl-3-methylimidazolium chloride as an ionic liquid [4]. Acetyl chloride represents a still more reactive agent of esterification. Acetylation of cellulose can be performed in dimethylformamide (DMF)/pyridine using an alkali or alkaline earth salt of acetic acid in the presence of *p*-toluenesulfonyl chloride [5]. Synthesis of cellulose acetate was also performed by the transesterification with ethylene diacetate via dissolving of cellulose in the *p*-formaldehyde/dimethyl sulfoxide (DMSO) at high temperatures [6]. Acid-catalyzed esterification reactions can promote the reaction yield by shifting the equilibrium reaction to the products. This phenomenon is attributed to the assisting of acids to the formation of acetyl cation CH_3CO^+ as the reactive intermediate. The esterification reaction with acetyl chloride showed high yields with tertiary amines such as triethylamine (TEA) or pyridine due to forming of acylium complex. 4-Dimethylaminopyridine (DMAP) is an efficient catalyst for the esterification reaction, especially in a homogeneous system with a nonpolar reaction medium [7]. For the acetylation of fibers, the preactivated cellulose is reacted with a large excess of acetic anhydride (Ac_2O) in the presence of acetic acid (HAc), usually with $HClO_4$ as the catalyst.

Also, Ac_2O vapor can be employed for the fiber acetylation, by adding some propionic or butyric anhydride to the vapor phase, obtaining the appropriately mixed ester, i.e., cellulose acetopropionate or acetobutyrate. Among the numerous nonderivatized solvent systems for cellulose, two systems including the solution in *N*,*N*-dimethylacetamide (DMA)/LiCl and a melt solution in *N*-ethylpyridinium chloride have been successfully employed for the acetylation of this polymer [8], indicating a preferential substitution at the C-6 position. Ac_2O/pyridine in the paraformaldehyde/DMSO solvent is the effective system for the acetylation of all the hydroxy end groups of the methylol side chains. The system afforded a high degree of substitution (DS) of the acetyl groups by transesterification of ethylene diacetate in the presence of natrium acetate at 90 °C [9]. Acetylation of cellulose in the chloral/DMF/pyridine system leads to the complete substitution of the hydroxyl groups by the acetal groups with a DS of 2.5 by Ac_2O or acetyl chloride [10]. Production of cellulose acetate from tosylcellulose (DS = 0.9–2.3) has been reported by the reaction with 3 mol of Ac_2O per mol of hydroxy groups in the presence of sodium acetate in pyridine at 60 °C [11]. This reaction can be performed with trimethylsilyl (TMS) cellulose (DS = 2) with an excess of Ac_2O [12]. Acetylation of the free hydroxyl groups was performed in a benzyl ether of cellulose with DS = 2; in benzene using Ac_2O catalyzed with TEA [13], an addition of

4-dimethylaminopyridine to the system promoted the DS of acetyl groups from 0.1 to 0.35. The reaction was also reported for nanocellulose [14].

Cellulose Formate

Formylation of cellulose for the first time was performed with DS values of about 2.5 using 98–100% formic acid at room temperature after a reaction time of about 2 weeks [15]. The rate of reaction was increased with the addition of H_2SO_4, HCl, or $ZnCl_2$. Phosphoric acid also can catalyze the reaction in water with a DS of about 0.6 [16]. A special approach was described by Vigo et al. for the synthesis of cellulose formate via reacting of cellulose with thionyl chloride in DMF [17].

Other Cellulose Alkylates

Cellulose esters of higher aliphatic acids were synthesized along the same methods as described for cellulose acetate such as employing the acid anhydride in the presence of the suitable catalyst or the acid chloride with a tertiary base. The propionylation of cellulose can be performed with the corresponding anhydride and an acid catalyst. For obtaining high DS, a cellulose suspension in dioxane/pyridine can be employed with propionic acid chloride for propionylation. The heterogeneous propionylation of cellulose was investigated with Farvardin and Howard using propionic acid, propionic anhydride, and a metal chloride as the catalyst in an aprotic solvent [18]. Acylation of cellulose with an aliphatic chain length of between three and eight carbon atoms can be carried out using a 2% cellulose solution in DMA/LiCl with 9% LiCl, and a mixture of the appropriate acid with its anhydride in the presence of *N*,*N*′-dimethylcyclohexylcarbodiimide (DCC) or pyrrolidinopyridine as the catalyst [19]. The propionylation of partially substituted methyl and ethyl celluloses to give stable ether esters has been performed by Guo and Gray [20].

The esterification with higher aliphatic acids is challenging and must be taken in the dry solvent. For such esterification, a preactivation of the polymer with an aliphatic amine is a good strategy for increasing DS. Esterification of microcrystalline cellulose with pelargonic acid chloride, up to a DS of 3, has been reported by Battista et al. [21]. A mixture of *p*-toluenesulfonyl chloride and the sodium carboxylate in a medium of DMF and pyridine was found to be effective in the preparation of higher cellulose esters [22]. Homogeneous transesterification of cellulose trinitrite by lauroyl chloride in a N_2O_4/DMF solution of cellulose was reported by Shimizu et al. [23].

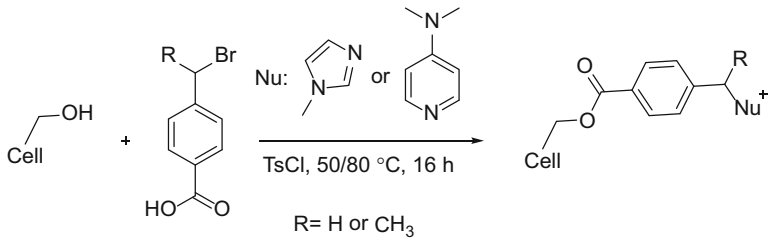
Palmitoyl ester of cellulose was prepared by the reaction of cellulose with the appropriate acid chloride without the presence of a solvent at a sufficiently high temperature [24]. In this "vacuum acid chloride technique," the HCl formed is eliminated from the system continuously by vacuum. The effects of fatty acid chain lengths and solvent on the esterification of cellulose with fatty acids are described [25]. The esterification of bacterial (and vegetable) cellulose fibers with a wide variety of anhydrides (acetic, butyric, hexanoic, and alkenyl succinic anhydrides) and hexanoyl chloride suspended in an ionic liquid, tetradecyltrihexylphosphonium bis(trifluoromethylsulfonyl)imide, [TDTHP][NTf_2], can be performed [26]. The esterification of cellulose can be performed in the gas phase. In a report, the reaction

of palmitoyl chloride vapors with aerogels of cellulose nanocrystals gave palmitate ester of the polymer [27]. Heterogeneous esterification of softwood cellulose nanofibers (CNF) using pyridine/tosyl chloride gives cellulose oleate [28].

Cellulose Aromatic Esters

Cellulose benzoate and phthalate are cellulose aromatic esters. Cellulose tribenzoate with a DS between 2.8 and 2.9 is obtained in a one-step reaction of the polymer with benzoyl chloride in the presence of pyridine [29]. Nitrobenzene as a solvent and pyridine as the catalyst were used for this reaction at 130–140 °C. In this approach, a monobenzoate could be conveniently prepared by reacting alkali cellulose with an appropriate amount of benzoyl chloride [30]. An unconventional route of synthesis has been reported by Isogai et al. who used ozonization of cellulose tribenzyl ether with DP of 1200 to produce a cellulose benzoate with DS of 2.5 and a DP of about 800 [31]. Derivatization of cellulose benzoates was performed with high DS using the appropriate free acids containing $–NO_2$, –Cl, or $–OCH_3$ in the presence of pyridine and *p*-toluenesulfonyl chloride [23]. Cellulose cinnamates with a DS of up to 3 have been synthesized by the reaction of cellulose dissolved in DMA/LiCl with cinnamoyl chloride in the presence of pyridine at 30–60 °C [32]. The esterification of cellulose with carboxylic acid can help to introduce ionic compounds on cellulose. As an example, the reaction of nanocellulose with benzoic acid which contains a leaving group such as bromide gave an intermediate for the reaction with 1-methylimidazole and 4-dimethylaminopyridine according to Scheme 1 [33].

Phthalic anhydride is generally employed for the esterification of cellulose in the presence of a basic catalyst for the phthaloylation of cellulose. The esterification of cellulose with the anhydrides of phthalic acid, nitrophthalic acid, and trimellitic acid in the presence of TEA and DMAP in DMSO was reported [34]. Cellulose acetophthalates are important commercial products, which are generally obtained by the reaction of cellulose acetate in the DS range between 1.7 and 2.5 with phthalic anhydride in the presence of a basic catalyst such as pyridine or TEA, in a dipolar aprotic or rather a nonpolar medium (DMSO, DMF, dioxane, acetone, benzene). Also, tetrahydro- and hexahydrophthalic acid anhydride have been introduced as esterifying agents in the presence of a catalyst such as TEA, pyridine, picoline, lutidine, DMAP, and 1,4-diazabicyclo-2,2,2-octane (DABCO).



Scheme 1 The loading of 1-methylimidazole and 4-dimethylaminopyridine on nanocellulose

Cellulose Esters with Amino Acids

The esterification reaction susceptibility of cellulose makes it possible to bind the polymer with the most of the carboxylic acids. The modifications of cellulose were reported with various hydrophilic (Gly, Ser), aliphatic (Ala, Val, Leu, Ile), and aromatic amino acids (Phe, Tyr, Trp). The carboxylic acid group of amino acids can be reacted with cellulose hydroxyl groups by the esterification reaction while this group is a neighbor of an amine group. It is shown that the aromatic amino acids, particularly Trp, enhanced cell spreading [35]. Modification of cellulose whiskers was reported with l-leucine amino acid via esterification reaction [36].

Cellulose Esters with Sulfonic Acid

Esters of cellulose can be formed also with sulfonic or phosphonic acid groups. Two important sulfonic acids are methylsulfonic acid, so-called mesylcellulose, and the esters of cellulose with *p*-toluenesulfonic acid, so-called tosylcellulose. The reaction of cellulose with a large excess of *p*-toluenesulfonyl chloride in pyridine at room temperature up to 80 °C led to the formation of tosylcellulose [37]. In a homogeneous system, tosyl chloride was employed in the presence of TEA as the base, for the tosylation of cellulose with a degree of polymerization (DP) between 280 and 5100, arriving at tosylcelluloses of DS values between 0.4 and 2.3 during 24 h at 8 °C [38].

Phenyl Carbamate of Cellulose

The reaction of cellulose with an excess amount of phenyl isocyanate in a dipolar aprotic medium in the presence of pyridine at 70–100 °C yields a cellulose tricarbanilate. The reaction system changes gradually from a heterogeneous one to a homogeneous one, and only negligible chain degradation has occurred in this process [39]. A homogeneous route to the preparation of cellulose tricarbanilate was reported by dissolving the sample in DMA/LiCl and its reaction with an adequate amount of phenyl isocyanate in the presence of pyridine as the catalyst [40]. Some derivatives of cellulose carbamate such as 3,5-dimethylphenyl carbamate residue in the C-2/C-3 positions and a 3,5-dichlorophenyl carbamate residue in the C-6 position were synthesized by Kaida and Okamoto [41].

Other Organic Esters of Cellulose

Cellulose, extracted from sugarcane bagasse, was successfully succinylated using DMAP as a catalyst in ionic liquid of 1-butyl-3-methylimidazolium [42]. The esterification of cellulose can be assisted to the immobilization of ligands capable of complexation with metal cations on the polymer. The esterification reaction of cellulose with citric acid gives cellulose citrate as a ligand for removal of copper pollutions [43].

1.1.2 Inorganic Esters of Cellulose

Some of the cellulose esters with inorganic compounds containing S, N, P, and B are introduced. The chemistry of these compounds is challenging due to the impossibility of isolation the products.

Cellulose Sulfuric Acid

The reaction of SO_3 or XSO_3H with the hydroxyl group of cellulose can lead to the formation of cellulose sulfuric acid (CSA). CSA can be converted to a neutral sodium salt soluble in water above a DS of 0.2–0.3. The synthesis of medium to high DS cellulose sulfates was performed with the SO_3/DMSO or the SO_3/DMF complex [44]. Most frequently H_2SO_4, SO_3, and $ClHSO_3$ were applied as the sulfonating agents of cellulose, which in some cases alcohols, amines, or inert media such as chlorinated hydrocarbons used for improving the yield.

After the first report about the reaction between cellulose and sulfuric acid, the reaction was improved in the presence of some reagents such as SO_3 and $ClSO_3H$, also SO_2Cl_2, FSO_3H, $ClSO_2–OC_2H_5$, $CH_3–CO–SO_4H$, and $NO–SO_4H$. Among these reagents, SO_3 and $ClSO_3H$ showed high activities. Sulfation of cellulose with SO_3/DMF in several solvent media was investigated in the presence of TEA, indicating a positive effect of the presence of TEA.

Cellulose Inorganic Ester Containing Nitrogen

Cellulose Nitrate

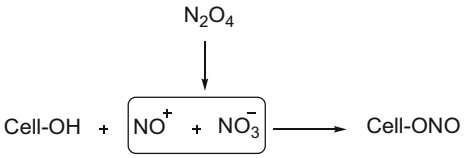
Cellulose nitrate had been prepared already in 1847 by reaction of the polymer with HNO_3 in the presence of H_2SO_4/H_2O [45]. This route is still of interest for the industrial production of cellulose nitrate. Nitration of cellulose was reported under different conditions [46]. The nitration systems of this report include $HNO_3/H_2SO_4/H_2O$, HNO_3/inorganic nitrate, HNO_3 vapor, HNO_3 vapor + NO_x, $HNO_3/H_3PO_4/P_2O_5$, N_2O_5, N_2O_5/CCl_4, HNO_3/CH_2Cl_2, $HNO_3/CH_3–NO_2$, $HNO_3/CH_3COOH/Ac_2O$, and HNO_3/propionic acid/butyric acid. High nitrogen contents, >14%, can be obtained without significant chain degradation by the systems HNO_3/CH_2Cl_2 at 0 to −30 °C, $HNO_3/H_3PO_4/P_2O_5$, and HNO_3/acetic acid/acetic anhydride. Also, nitronium salts like $[NO_2]^+[BF_4]^-$ and KNO_3 in 98% H_2SO_4 can make a little nitration of cellulose [47]. Formation of cellulose nitrate was also claimed to occur on heating a solution of cellulose in N_2O_4/DMF [48]. Cellulose mixture with 0.5 M $[NO_2]^+[BF_4]^-$ in sulfolan, as well as with KNO_3 in 98% H_2SO_4, gives cellulose nitrate [47].

Cellulose Nitrite

The nitrite of cellulose cannot be synthesized by esterification with HNO_2 due to the low acidity and the low stability of nitrous acid. However, a highly substituted nitrite of cellulose can be prepared by the reaction of cellulose with N_2O_4, NOCl, or several salts like nitrosylic compounds under anhydrous conditions in a suitable dipolar aprotic solvent like DMF. The general reaction for the preparation of cellulose nitrite from N_2O_4 is according to Scheme 2.

The O-6 position is preferred for the modification to nitrite formation. Some of the important reagents for the esterification of cellulose with nitrite are N_2O_4, NOCl, $NOSO_4H$, $NOBF_4$, and $NOSbCl_6$ [49].

Scheme 2 Synthesis of cellulose nitrite from N_2O_4



Cellulose Inorganic Esters Containing P

The covalent binding of phosphorus to the cellulose gives one of cellulose phosphate Cell-O-P(O)$(OH)_2$, cellulose phosphite Cell-O-P$(OH)_2$, and cellulose phosphonic acid groups Cell-P(O)$(OH)_2$.

Cellulose Phosphate

Pentavalent phosphorus compounds such as H_3PO_4, P_2O_5, and $POCl_3$ are the most frequently used reagents for phosphorylation of cellulose. Compared to the corresponding compounds of hexavalent sulfur, these phosphorylating agents which usually give anionic cellulose phosphates show a lower reactivity in the esterification and lead to much less chain degradation during this process. Concentrated orthophosphoric acid has been widely used as an effective phosphating agent, and various procedures have been reported for the synthesis of cellulose phosphates with phosphorus contents of about 10% [50]. Water-soluble cellulose phosphates of rather high DP can be obtained with water-free H_3PO_4, in which P_2O_5 was employed for increasing phosphorylation yield [51]. A system including H_3PO_4/P_2O_5/DMSO, and also with ternary systems of H_3PO_4/P_2O_5/aliphatic alcohols with 4 to 8 C atoms, produced water-soluble cellulose phosphates [51]. The reaction of cellulose with a melt solution of H_3PO_4 and urea gives a soluble, but strongly degraded, cellulose monophosphate monoammonium salt [52]. Phosphorus oxychloride ($POCl_3$), as an effective phosphating agent for cellulose, in the reaction with a cellulose suspension in DMF or pyridine gives cellulose phosphate with some by-product such as chlorinated cellulose. Phosphorylation of cellulose hydrogels was reported with a mixture of phosphorus pentoxide, triethyl phosphate, and phosphoric acid [53].

Cellulose Phosphite

Cellulose phosphite can be prepared by the reaction of cellulose with a trivalent phosphorus such as PCl_3 [54] or by transesterification with dimethyl phosphite, arriving at hydrolysis-susceptible phosphite esters of cellulose [55]. Cellulose phosphites have also been synthesized, employing mixed anhydrides of hydrophosphoric and acetic acid and arriving at phosphorus contents of up to 8% [56].

Cellulose Phosphonic Acid

Preparation of cellulose phosphonates, the phosphorus directly bound to a C atom of the cellulose, is either an esterification with methyl or phenylphosphonic anhydride [57] or a two-step reaction consisting of the chlorination of cellulose

with $SOCl_2$ to give chlorodesoxycellulose with a high Cl content (up to 16%) and the subsequent reaction of this compound with triethylphosphite to the cellulose phosphonate via an Arbuzov rearrangement. 3-(Hydroxyphenylphosphinyl)-propanoic acid (3-HPP) esters of cellulose were synthesized in DMA/LiCl homogeneously by the method of in situ activation with *p*-toluenesulfonyl chloride [58].

Cellulose Borates

Boron-containing cellulose derivatives are interesting due to unique properties such as flame retardancy or heat stability. The synthesis of cellulose borates was reported by two approaches including (i) the direct esterification of cellulosic hydroxy groups with orthoboric or metaboric acid and (ii) a transesterification of cellulose with boronic acid esters of lower aliphatic alcohols (boron alkoxides). A direct borylation of cellulosic hydroxy groups can be performed with ortho- or metaboric acid in a melt of urea at 150–200 °C [59]. The preparation of a mixed borate/phosphate cellulose has been described by subsequent reaction of the cellulose borate with H_3PO_3/urea and with $H_4P_2O_7$ or HPO_3/urea in the temperature range 100–200 °C [60].

1.2 Desoxycelluloses

Desoxycelluloses are cellulose derivatives obtained from the substitution of a hydroxy group by halogen, sulfur, nitrogen, or even carbon. Cellulose esters, tosylcellulose or mesylcellulose, are efficient intermediates for the synthesis of desoxycelluloses. The desoxycelluloses are produced from the reaction of these intermediates with inorganic salts containing the group to be introduced as the nucleophilic reagent in this displacement reaction. The use of tetraalkylammonium fluorides proved to be successful for reaching a high degree of substitution [61]. Chlorodesoxycellulose is most conveniently synthesized from the reaction of cellulose with $SOCl_2$ in pyridine [62], DMF [63], CCl_4 [64], or $CHCl_3$. Carre and Manclere [62] reported the synthesis of cyclic sulfide-modified cellulose. Also, SO_2Cl_2 can be applied to prepare chlorodesoxycelluloses with DS values of 0.4–0.8 [65]. A homogeneous approach to the preparation of chlorodesoxycellulose was reported by Furuhata et al. [66], starting from a solution of the polymer in DMA/LiCl and reacting with *N*-chlorosuccinimide and triphenylphosphine. A homogeneous chlorination of cellulose can also be performed with methylsulfuryl chloride after dissolving the polymer in the chloral/DMF system. Fluorodesoxycellulose was prepared via a treatment of mesylcellulose with an aqueous NaF solution [67]. Bromodesoxycellulose can be prepared by *N*-bromosuccinimide and triphenylphosphine [68]. Some of the routes for the synthesis of desoxycelluloses from tosyl- to mesylcellulose were described in Table 1.

Tosylcellulose is also applied as the starting material for the preparation of aminodesoxycellulose by reacting with NH_3, aliphatic amines, or hydrazine [69].

Table 1 Preparation of desoxycelluloses via tosyl- or mesylcellulose

Entry	Desoxy group	Tosyl- or mesylcellulose	Reagents and conditions
1	Fluoro-	mesylcellulose	NaF in H_2O
2	Chloro-	tosylcellulose	Tosyl chloride and pyridine at high temperature
	Chloro-	tosylcellulose	LiCl in acetylacetone (2 h at 130 °C)
3	Bromo-	mesylcellulose	NaBr in H_2O
	Bromo-	tosylcellulose	NaBr in acetylacetone (2 h at 130 °C)
4	Iodo-	tosylcellulose and mesylcellulose	NaI in acetylacetone (2 h at 130 °C)
5	Mercapto-	tosylcellulose	H_2S in pyridine (8 h at 40 °C, then 70 h at room temperature)
	Mercapto-	tosylcellulose	$Na_2S_2O_3$ in DMSO
6	Cyano-	tosylcellulose	KCN in DMF or methanol (100–150 °C)
7	Thiocyanato-	tosylcellulose	NaSCN in acetonylacetone (11 h at 110 °C)
8	Azido-	tosylcellulose	NaN_3 in DMSO (110–130 °C)

1.3 Cellulose Ethers

Cellulose ether was prepared for the first time in 1905 by Suida, who reacted the cellulose with dimethyl sulfate to give a methylcellulose. Later, some other important classes of cellulose ethers such as carboxymethyl cellulose, benzyl cellulose, or hydroxyethyl cellulose had been introduced. In the early 1920s, industrial production of carboxymethyl cellulose (CMC) started in Germany. Two important routes are introduced for the production of cellulose ethers on the large scale:

(i) The reaction of hydroxy groups of cellulose with an alkyl chloride in the presence of strong alkali metal hydroxides, according to the Williamson ether synthesis
(ii) The ring-opening reaction of an alkylene oxide with the hydroxy groups of cellulose, which is catalyzed by alkali metal hydroxides

Also various silyl ethers have been synthesized by the reaction of cellulose especially with trialkylchlorosilanes.

1.3.1 Aliphatic Ethers of Cellulose

Most important aliphatic ethers of cellulose are methylcellulose, CMC, and hydroxyethyl cellulose (HEC).

Alkyl Ethers of Cellulose

As the most important compound from alkyl ether category, methylcellulose is commercially produced by a Williamson reaction of alkali cellulose with gaseous or liquid CH_3Cl. The etherification of cellulose in the presence of alkali hydroxide is accompanied by the hydrolysis of methyl chloride with the water. Methylation of

cellulose by the Williamson reaction is generally carried out at elevated temperature with cellulose in the solid state. Some of the systems employed in laboratory methylation of cellulose include DMSO/NaOH/CH_3I [70], DMSO/LiH/CH_3I [71], DMF, THF/NaH/CH_3I [72], CH_2Cl_2/2,6-di-i-butylpyridine $(CH_3)_3O^+[BF4]^-$ [73], and $(CH_3)_3PO_4$/2,6-di-*t*-butylpyridine/$CF_3SO_3CH_3$ (methyl triflate) [73]. Instead of methyl chloride, also methyl iodide, dimethyl sulfate, diazomethane, or special agents such as trimethyloxonium tetrafluoroborate, or methyl triflate can be used. NaH or LiH, metallic Na dispersed in an ammonia, and di-*t*-butylpyridine are bases applicable in this reaction. Methylcellulose has also been synthesized in aqueous solutions of tetraalkylammonium hydroxides [74]. Some of the methylation systems of cellulose are CH_3I/NaH in THF and CH_3I/powdered NaOH in DMSO [75].

Ethylation of cellulose has been performed by reacting alkali cellulose with ethyl chloride, arriving at a substitution pattern with about equal partial DS at C-2 and C-6 and again a low degree of etherification at C-3 [76]. Propylation of cellulose required either a previous partial methylation for "widening" the cellulose structure or employing a tetraalkylammonium hydroxide of high swelling power in aqueous solution as the base and reaction medium [77].

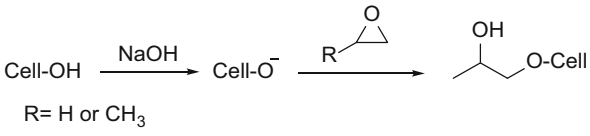
The preparation of long-chain cellulose alkyl ethers was reported in nonaqueous system by reaction of cellulose acetate with the appropriate alkyl bromide in the presence of NaOH in DMSO [78]. Blasutto (1995) reported the preparation of long-chain alkyl ethers from the reaction of cellulose with appropriate alkyl bromide in isopropanol or in DMSO in the presence of NaOH or NaH [79]. Recently, etherification of cellulose with chloroacetic acid has attracted attentions, since cellulose acetic acid as the product has the ability of more modification. Modification of cellulose acetic acid with *D*-penicillamine gave a good cellulose-based ligand for grafting of Co(II) [80]. Cellulose acetic acid was also modified with ethylenediamine for preparation of a Pd ligand [81].

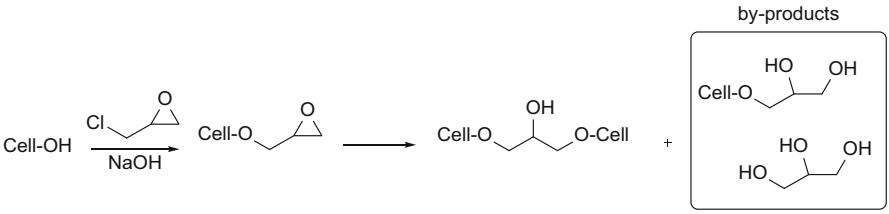
Hydroxyalkyl Ethers of Cellulose

Two commercially relevant derivatives of cellulose are hydroxyethyl cellulose (HEC) and hydroxypropyl cellulose (HPC), which are prepared by the reaction of cellulose with ethylene oxide and propylene oxide, respectively (Scheme 3).

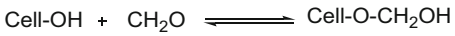
The acid-catalyzed cleavage of the epoxy ring for alkylation of cellulose leads to the homopolymerization of epoxy instead of the intended etherification. Hydroxyalkylation of cellulose using basic catalyst is generally performed with the weight ratio of NaOH/cellulose varying within the wide limits of between

Scheme 3 Preparation of HEC and HPC





Scheme 4 The reaction of cellulose with epichlorohydrin



Scheme 5 The reaction of cellulose with formaldehyde

0.3:1 and 1:1 and that of H_2O/cellulose between 1.2:1 and 3.5:1. In this route, an excess of a fairly inert diluent like *i*-propanol, *t*-butanol, or acetone is employed in hydroxyethylation [82].

Etherification with Epichlorohydrin

Epichlorohyrin having two electrophilic sites acts as a cross-linking agent of cellulose in an aqueous alkaline medium with some by-products. This process is described in Scheme 4.

For this reaction catalytic amounts of NaOH required for epoxy ring cleavage and the stoichiometric amount of 1 mol/mol of epichlorohydrin are necessary for the epoxide formation [83]. Etherification with epichlorohydrin has also been performed with cellulose dissolved in DMA/LiCl and powdered NaOH or with LiOH as the base [84].

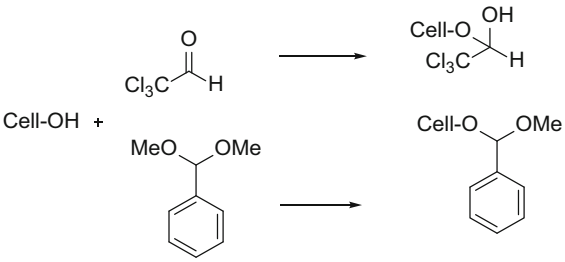
Hydroxymethyl Cellulose

Hydroxymethyl ("methylol") cellulose can be produced from the reaction of cellulose with a large excess of formaldehyde above 80 °C or, more comfortably, with paraformaldehyde in DMSO at 135–140 °C (Scheme 5). A methylolated cellulose preparation was examined in various solvents at elevated temperature with gaseous CH_2O, as well as with paraformaldehyde [85]. DMSO, DMA/LiCl, and DMF/LiCl are good solvents for the preparation of methylol cellulose.

The synthesis of a methylol cellulose octadecylcarbamate was reported by the reaction of cellulose with octadecyl isocyanate in the presence of stannic octoate at 50 °C in DMF/LiCl as the solvent [86].

Some of the interesting derivatives of methylol celluloses were reported using reagents with similar behavior with formaldehyde such as trichloroacetaldehyde (chloral) and hemiacetals (Scheme 6) [87].

Scheme 6 The reaction of cellulose with chloral and hemiacetal



Cyanoethyl Cellulose

Cyanoethylation of cellulose proceeds via a Michael addition of partially anionized cellulose hydroxyl group to an activated C=C bond of acrylonitrile. Bikales reported a procedure for the preparation of a fibrous cyanoethyl cellulose with DS = 2.75 (12.6% N) from regenerated cellulose with acrylonitrile and aqueous NaOH at 50 °C [88]. Wide studies were performed on the cyanoethylation of cellulose. Cyanoethylation of cellulose has been reported as an equilibrium reaction with the cellulose either by simultaneous (one-step process) or by subsequent (two-step process) addition of the components aqueous NaOH and acrylonitrile at a temperature between 30 °C and 50 °C, within some hours. The reaction rate of cyanoethylation can be improved significantly by a preactivation of the cellulose sample by 18% NaOH or by pretreatment with liquid NH_3 and could also be enhanced by the addition of DMSO to the system for increasing the solubility of acrylonitrile [89]. *N*-Methylmorpholine also can play a base role for the cyanoethylation of cellulose [90]. The nitrile group of cyanoethyl cellulose can be reduced to an aminopropyl substituent with diborane [91]. An amidoxime can be prepared from the reaction of hydroxylamine with carbamoylethyl cellulose in a neutral aqueous system at 70 °C [92].

Aminoalkylcellulose

The reaction of cellulose with aziridine gives the aminoethylcellulose in an aqueous alkaline medium. The route is preceded by employing cellulose suspension in toluene and reacting it with aziridine in the presence of benzyl chloride in an autoclave at 70 °C for 10 h. Aminoethylation of cellulose and cellulose derivatives was reported with ethylenimine, 2-methylethylenimine, 2,2-dimethylethylenimine, trimethylethylenimine, 2-phenylethylenimine, 2-(*p*-tolyl) ethylenirnine, Z-biphenylethylenimine, 2-(*p*-aminophenyl)ethylenimine, and 2-(2,4-dinitrophenyl)ethylenimine [93]. Figure 1 shows some of the starting materials for the reaction with cellulose to produce aminoalkylcellulose.

Sheets of bacterial cellulose were chemically modified with glycidyltrimethylammonium chloride in the presence of sodium hydroxide to introduce a positively charged amine to cellulose [94]. DABCO-cellulose nanofibers can be prepared via the activation of cellulose with tosyl group and subsequent reaction of cellulose tosylate with DABCO [95]. Immobilizing of amine groups on cellulose can be

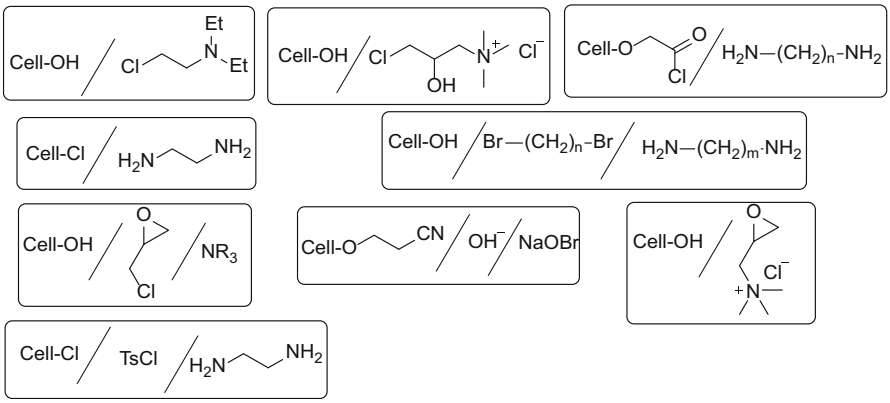


Fig. 1 Some of the starting materials for the reaction with cellulose to produce aminoalkylcellulose

improved metal complex with the modified cellulose. Modification of cellulose can be performed with glycidyl methacrylate (GMA) and diethylenetriamine to deposition of amine groups on cellulose for the preparation of Cu(II) and Hg(II) absorbent [96]. Keshipour et al. modified cellulose with ethylenediamine to improve cellulose activity in Pd or Co complexation for the synthesis of efficient catalyst for coupling [97], cycloaddition [98], and oxidation reactions [99, 100].

Sulfoalkyl and Thioalkyl Ethers of Cellulose

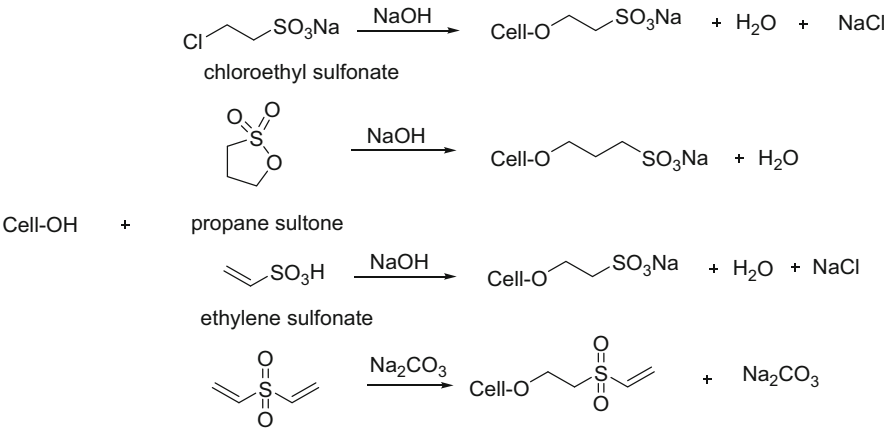
This category of cellulose derivatives is synthesized from the reaction of alkali cellulose with chloroalkane sulfonate, propane sultone, or ethylene sulfonate (Scheme 7) [101].

The order of reactivity of the agents for this reaction is propane sulfone < chloroalkyl sulfonate < vinyl sulfonate. Other reagents for the sulfoalkylation are $Cl–CH_2SO_3Na$, $HSO_3–O–CH_2–CH_2SO_3H$, and $CH_2=CH–SO_2–CH=CH_2$.

Thioalkyl cellulose synthesis can be performed via thiol-ene click reaction in two steps including the reaction of cellulose with allyl chloride to give allyl cellulose and then the reaction of allyl cellulose with a sulfide [102]. The thiol-ene reaction also was reported with vinyltrimethoxysilane and 3-mercaptopropyltrimethoxysilane [103].

Arylalkyl Ethers of Cellulose

Benzyl cellulose as the most important ether of this type was first synthesized by Leuchs in 1917. The chemical library of arylmethyl ethers was developed by the introduction of substitute that contained different types of alkyl residues [104], halogen substituents [105], and functional groups like methoxy, nitro, and amino groups mainly in para position of the benzyl units or in some cases aryl groups other than phenyl [106]. The synthesis pathway consists in the reaction of cellulose with



Scheme 7 The procedures for the preparation of sulfoalkyl ethers of cellulose

the corresponding arylmethyl halogenides in presence of a base [107]. The reaction proceeds in water using sodium hydroxide [108].

Triphenylmethyl ("trityl") cellulose as the most important ether of a class of organosoluble aryl cellulose ethers was formed by the reaction of phenylmethyl halides with cellulose in the presence of an organic base [109]. Some similar compounds such as benzhydryl (diphenylmethyl)cellulose, benzyl(phenylmethyl)cellulose, and phenylcellulose were generally prepared via this route. Heterogeneous tritylation of decrystallized cellulose was reported using pyridine by treatment with 15% aqueous ammonia and yields colorless products with DS values from 0.81 to 1.21 [110].

1.3.2 Aryl Ethers of Cellulose

The introduction of an aromatic group via an ether bond leads to cellulose aryl ethers, especially to phenyl and substituted phenylcelluloses. The reaction can be performed via the etherification of cellulose with activated aryl halogenides or the displacement reaction of cellulose tosylate with corresponding phenolates. Various phenyl derivatives were employed for this reaction such as phenyl containing nitro, carboxylic acid, amine, bromide, chloride, etc. [60].

1.3.3 Silyl Ethers of Cellulose

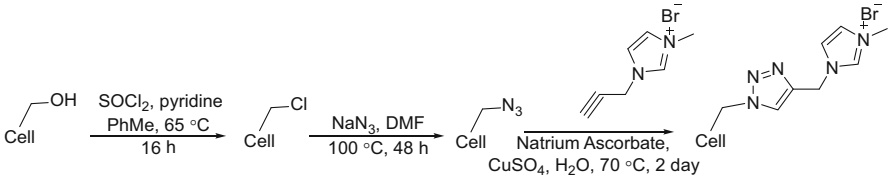
The reaction of cellulose with TMS-Cl in the presence of pyridine has been reported for the first time by Schuyten et al. [111]. Silylation of cellulose with TMS-Cl and pyridine gave TMS cellulose with DS values of 2.4 to 3.0. The reaction was investigated in some solvents such as xylene, toluene, and petroleum ether, in which short reaction times in toluene and mild reaction conditions in petroleum ether were obtained. In addition, NH_3 instead of pyridine improved the reaction conditions [112]. Klebe and Finkbeiner have synthesized cyanopropyldimethyl-, phenyldimethyl-, and diphenylmethylsilylcelluloses. Hexamethyldisilazane is a convenient reagent for the trimethylsilylation of cellulose [113]. The reaction proceeded

in polar solvents in the presence of catalyzers such as NH_4Cl or TMS-Cl/pyridine. Cellulose activated with ammonia at 80 °C has been reacted with the thexyldimethylsilylamine, prepared from the reaction of thexyldimethylchlorosilane (TDMSCl) and *N*-methylpyrrolidone (NMP) to give corresponding silylated cellulose. The chemical modification of cellulose with silanes contains another functional group which assisted the loading of the desired functionality on cellulose. For example, the modification of cellulose paper with 3-aminopropyltrimethoxysilane leads to the deposition of an amine group on cellulose [114].

1.4 Heterocycles Grafted on Cellulose

Heterocyclic-nanocellulosic derivatives were prepared by surface modification of cellulose nanocrystals with 4-chloro-2,2′:6′,2″-terpyridine and subsequent coupling with other terpyridine-functionalized derivatives via Ru^{III}/Ru^{II} reduction [115]. Alkynylated cellulose nanocrystals were modified with a series of reactive GAP (glycidyl azide polymer)/PTPB (propargyl-terminated polybutadiene) nanocomposites by the Huisgen click chemistry [116]. In this reaction, cellulose contains alkyne group which reacted with the polymers containing azide groups to give triazide cycles. Coumarine, as one of the important pharmaceutical scaffolds, was introduced to the cellulose structure via chemical bonding to the hydroxyl group of cellulose. For performing the reaction, at first the acyl chloride group was created on coumarine, and then the new group reacted with the hydroxyl group of cellulose [117]. For loading of the imidazolium group on cellulose nanocrystals, the procedure described in Scheme 8 was performed [118].

A similar strategy using introducing of azide group to cellulose and subsequent reaction of azido cellulose with an alkyne was described [119]. The synthesis of triazide heterocycle on cellulose can be performed by introducing an alkyne group on cellulose and cyclization of the alkyne with an alkyl azide [120]. Chemical modification of cellulose with triazine derivative, 2,4,6-tri-[(2-hydroxy-3-trimethyl-ammonium) propyl]-1,3,5-triazine chloride (Tri-HTAC), was also reported. Tri-HTAC under reaction with NaOH produces a terminal epoxide, in which ring opening occurred under nucleophilic attack of cellulose [121]. Binding of a macrocyclic compound was also investigated, which phthalocyanine-Co(II) [122] and *N*-doped graphene quantum dots [123] were chemically attached to cellulose surface.



Scheme 8 Loading of imidazolium on cellulose nanocrystals

2 Polymers Grafted on Cellulose

The modification of cellulose can be performed with absorbent polymers. Modification of microfibrillated cellulose (MFC) by hydroxycarbonate apatite (HAP) or epoxy gives nanostructured adsorbents for the removal of hydrogen sulfide (H_2S) from the aqueous solutions [124].

2.1 Atom Transfer Radical Polymerization (ATRP) of Cellulose

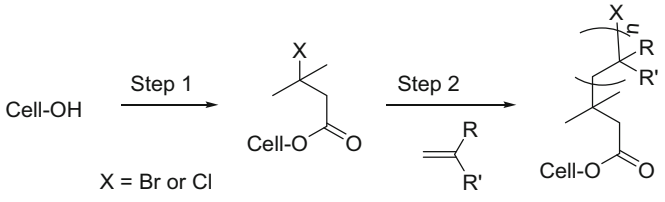
ATRP, as one of the most popular living/controlled polymerizations [125], is an important approach for the modification of cellulose. In ATRP, the radicals or the active species are generated through a reversible redox process undergo one electron oxidation give an active intermediate for the polymerization. The applications of ATRP for surface graft modification of cellulosic materials were first reported by Carlmark and Malmstom [126]. The general ATRP reaction on the cellulosic material was shown in Scheme 9.

Various functional groups were immobilized on cellulose and cellulose derivatives to perform an ATRP. Vinyl groups are one of the interesting functionalities to initiate an ATRP, which is widely studied. Table 2 gives a summary of the vinyl group as the cellulose ATRP initiator. These ATRPs were initiated by cellulose-X initiators and catalyzed with copper salts in the presence of various amine-type ligands. Table 2 shows the ATRP methods reported for the polymer loading on cellulosic materials.

The ATRP can be performed in both heterogeneous and homogeneous reactions, and the homopolymerization is effectively avoided since the anchored haloacyl groups are the only initiating sites in the system.

2.2 Reversible Addition-Fragmentation Chain Transfer (RAFT) of Cellulose

RAFT polymerization was first reported by Chiefari et al. [172] and developed as MADIX polymerization by Charmot et al. [173]. In both cases, a small amount of dithioester was introduced as chain transfer agent (CTA) in the classic free radical



Scheme 9 General ATRP reaction on cellulose

Table 2 Polymer-grafted cellulosic materials prepared via ATRP method

Cellulose derivative	Monomer	Initiator	Catalyst	Reaction conditions	Ref.
Cellulose	St, MMA, MAm, AcM	-Cl	CuBr/DPE	DMF, 130 °C	[127]
Cellulose	NIPAM	-Br	CuBr/PMDETA	DMF, r.t.	[128]
Cellulose	DMAam		CuCl/PMDETA	DMSO, 80 °C	[129, 130]
Cellulose	tBA		CuBr/PMDETA	DMF, 75 °C	[131]
Cellulose	DMAEMA		CuBr/PMDETA	DMF, 60 °C	[132]
Cellulose	MMA, St		CuCl/BPy	DMF, butanone, DMF/H_2O	[133]
Cellulose				Dioxane, butanone/toluene 40–110 °C	
Cellulose	MPC		CuBr/BPy	DMSO/MeOH, 40 °C	[134]
Cellulose	MMA	-Cl	CuBr/BPy	BMIMCl, 90 °C	[135]
Cellulose	EMO, MMA		CuBr(CuCl)/TEMED	DMF. 130, 70 °C	[136]
Cellulose	MMA		$CuBr_2$/TEMED/AsAc	DMAc, 50–70 °C	[137]
Cellulose	NIPAm		CuCl/Me_6TREN	DMF/H_2O, 80 °C	[138]
Cellulose microfibril	BA	-Br	CuBr/BPy, CuBr/PMDETA	DMF, toluene 90 °C	[139]
Cellulose membrane	AA NIPAm	-Br	NaOH/NaCl/CuCl/BPy CuCl/BPy	H_2O, r.t.	[140]
Cellulose membrane	PEGMA		CuCl/$CuCl_2$/BPy	H_2O, r.t.	[141]
Cellulose membrane	DMVSA		CuBr/BPy	MeOH/H_2O, 25 °C	[142]
Cellulose membrane	GMA		CuBr/BPy	DMF, H_2O, r.t.	[143]
Cellulose membrane	AA		CuCl/BPy	H_2O, 45 °C	[144]
Cellulose membrane	DMAEMA		$CuBr_2$/PMDETA/AsAc	MeOH/H_2O, 25 °C	[145]
Cellulose membrane	DMVSA, DMMSA, MPC		CuBr/BPy	MeOH/H_2O, r.t.	[146]
Cellulose membrane	GMA		CuCl/BPy	2-Propanol, 40 °C	[147]
Cellulose membrane	MA		CuBr/Me_6TREN	Ethyl acetate, r.t.	[148]
Cellulose membrane	NIPAm, DEAEMA		CuBr/BPy/Cu^0	MeOH, 40 °C	[149]
Cellulose membrane	AA		NaOH/NaCl/CuCl/Me_4Cyclam	H_2O, r.t.	[150]
Cellulose membrane	DMAEMA		CuCl/BPy	DMSO, r.t.	[151]

(*continued*)

Table 2 (continued)

Cellulose derivative	Monomer	Initiator	Catalyst	Reaction conditions	Ref.
Cellulose membrane	DMAEMA		$CuCl_2$/HMTEMA/AsAc	2-Propanol, 40 °C	[152]
Cellulose membrane	NASS		CuBr/BPy	MeOH/H_2O, 30 °C	[153]
CNCs	St	-Br	CuBr/HMTETA	In bulk, 110 °C	[154]
CNCs	NIPAm		CuBr/PMDETA	MeOH/H_2O, r.t.	[155]
CNCs	DMAEMA		CuBr/HMTETA	MeOH, 55 °C	[156]
CNCs	AEM, AEMA		CuBr/PMDETA	H_2O/MeOH	[157]
CNCs	St		CuBr/PMDETA	Anisole, 100 °C	[158]
CNCs	St	-Br	CuBr/PMDETA	TEA, DMF, 100 °C	[159]
MCC	MA	-Br	CuBr/Me_6TREN	Ethyl acetate, r.t.	[148]
MCC	Isoprene		$CuBr_2$/Me_6TREN/Cu^0	DMF/dioxane, 130 °C	[160]
MCC			$CuBr_2$/PMDETA/Cu^0		
MCC			$CuBr_2$/BPy/Cu^0		
Cellulose fiber	MeDMA	-Br	CuBr/BPy	H_2O, 20, 40, 70 °C	[161]
Cellulose fiber	MA, HEMA		CuBr/Me_6TREN, CuCl/$CuCl_2$/BPy.	Ethyl acetate, H_2O, r.t.	[126]
Cotton	EA	-Br	CuBr/$CuBr_2$/PMDETA	Anisole, in bulk, 90, 100 °C	[162]
Cotton	St				
Cotton	AA-Na		CuBr/$CuBr_2$/HMTETA	DMF, 45 °C	[163]
Cotton	GMA		CuBr/$CuBr_2$/PMDETA	H_2O, 30 °C	
Filter paper	MMA, St, GMA	-Br	$CuBr_2$/PMDETA/AsAc	Anisole, 30, 100, 0 °C	[164]
Filter paper	NIPAAm, 4VP, GMA	-Br, -Cl	CuCl/$CuCl_2$/Me_6TREN	MeOH/H_2O 30, 50 °C	[165]
Filter paper			CuCl/$CuBr_2$/PMDETA	2-Propanol, toluene, r.t.	
Filter paper	11OCB-MA	-Br	CuBr/PMDETA	Toluene, 100 °C	[166]
Filter paper	MA		CuBr/Me_6TREN	Ethyl acetate, r.t.	[148]
Filter paper	GMA		CuCl/$CuBr_2$/PMDETA	Toluene, 30 °C	[167]
Filter paper	*t*BA		$CuBr_2$/PMDETA/EBiB	Acetone, 60 °C	[168]
Ramie fiber	MMA	-Br	CuBr/$CuBr_2$/PMDETA/EBiB	THF, 30 °C	[169]
Ramie fiber	DMAEMA		CuCl/1,10-phenanthroline	Acetone/H_2O, 30 °C	[170]
Jute fiber	St	-Br	CuBr/PMDETA	Xylene, 110 °C	[171]
Lyocell fiber	MA	-Br	CuBr/Me_6TREN	Ethyl acetate, r.t.	[148]

See references to observe the abbreviations

system. RAFT agents are thiocarbonylthio moieties which are susceptible to undergo radical addition. Two important groups in the RAFT polymerization are R and Z, in which the R group initiates the growth of polymeric chains and the Z group activates the thiocarbonyl bond toward radical addition and then stabilizes the resultant adduct radical. The propagating radical is added to the C=S moiety of the RAFT agent to form an intermediate radical that will fragment back either to the original propagating radical or to a new carbon-centered radical. In the RAFT polymerization of cellulose at first, CTA is attached to cellulose. Then, the reaction completes with the binding of monomer assisted with an initiator such as AIBN. Table 3 shows some RAFT for cellulosic materials.

Table 3 Polymer-grafted cellulosic materials prepared via RAFT polymerization method

Cellulosic material	Chain transfer agents	Monomer	Initiator	Reaction conditions	Ref.
Filter paper	BPDF	IBA	AIBN	$CHCl_3$/THF, r.t.	[174]
Filter paper	CPADB, BSPAC	SS	ACPA or γ-ray	H_2O/EtOH, 70 °C	[175]
Filter paper	MCPDB	DMAEMA, St	AIBN	Toluene, 60 °C	[176]
Filter paper	MCPDB	DMAEMA	AIBN	EtOH, r.t.	[177]
Filter paper	CPDA	St	γ-ray	EtOH, toluene, dioxin/H_2O, r.t.	[178]
Filter paper	CPDB	GMA	γ-ray	DMF	[179]
Cotton	MCPDB	St	AIBN	Toluene, 60 °C	[180]
Cotton fabric	MCPDB	St, MMA, MA, DMA	AIBN	In bulk, 60 °C	[181, 182]
Ramie fibers	ECPDB (free CTA)	MMA,MA, St, *p*-chlorostyrene	AIBN	THF, 60 °C	[183, 184]
Ramie fibers		TFEMA	AIBN	Supercritical CO_2, 70 °C	[185]
Wood fibers	CA	EECX VAc, St, VBC	AIBN	In bulk, 90 °C	[186]
Nanofibers	CPADB (free CTA)	VBTAC	ACPA	Buffer, 70 °C	[187]
CNCs	DDMAT	NIPAm, AA	AIBN	Dioxane, 70 °C	[188]
Cellulose membrane	CPADB	DMAPS	AIBN	MeOH, 70 °C	[189]
Filter paper	BSPA	St	AIBN	MP	[190]
	BSPAC	St, HEMA	AIBN	MP, 60 °C	[191]
HPC, MC	S-sec propionic Acid xanthate	VAc	AIBN	DMF, 68 °C	[192]
EHEC	BSPA	AAM	ACPA	DMSO, 70 °C	[193]

(*continued*)

Table 3 (continued)

Cellulosic material	Chain transfer agents	Monomer	Initiator	Reaction conditions	Ref.
HPC	PABTC	NIPAAm, EA	AIBN	Dioxane, DMAc, 60 °C	[194]
Cellulose	DDMATC	Amino acid acrylate, (A-(L) Ala-OH, A-(L) Pro-OH, A-(L) Glu-OH)	AIBN	DMAc/THF, 80 °C	[195]
Cellulose	ECDPB	MMA	AIBN	BMIMCl 60 °C	[196]
Cellulose	Trithiocarbonate	NIPAm, DEAAm	AIBN	DMF, 70 °C	[197]

See references to observe the abbreviations

2.3 Nitroxide-Mediated Radical Polymerization (NMP) of Cellulose

NMP is based on the use of a stable nitroxide radical, such as (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO), which is the more commonly used nitroxides. In NMP approach, the propagating species (P_n°) can propagate by reacting with a monomer (M), or it can terminate with other radicals [198]. NMP is usually undertaken at high temperatures.

Nitroxide-mediated grafting of cellulose under homogeneous conditions was first reported by Daly et al. [199]. In their approach, carbonates of *N*-hydroxypyridine-2-thione have first immobilized onto hydroxypropyl cellulose (HPC) backbones and subsequently irradiated the cellulose derivatives in the presence of an excess of TEMPO and styrene (St) to form St-TEMPO adducts promoting the preparation of HPC-g-PS graft copolymers. Nitroxide-mediated polymerization was reported for the synthesis of cellulose-grafted polystyrene (PSt) and poly(methyl methacrylate) (PMMA) as the branches. For this purpose, cellulose was acetylated by 2-bromoisobutyryl bromide, and then the bromine group was converted to 4-oxy-2,2,6,6-tetramethylpiperidin-1-oxyl group by a substitution nucleophilic reaction. The produced intermediate was subsequently used in controlled graft and block copolymerizations of St and MMA monomers to yield cellulose-grafted (g)-PSt and cellulose-g-(PMMA-b-PSt) [200]. Poly(lactic acid)/cellulose nanofiber (PLA/CNF) composites were prepared by TEMPO-mediated oxidation of CNF. MCNF was synthesized by the controlled amidation of CNF with *cis*-9-octadecenylamine (OA) that resulted in PLA/MCNF composites with improved mechanical properties and tunable elongation compared to PLA/CNF [201]. The CNC surface was also functionalized with the nitroxide SG1 (4-(diethoxyphosphinyl)-2,2,5,5-tetramethyl-3-azahexane-*N*-oxyl), yielding a CNC-macroalkoxyamine. Poly(methyl acrylate) and poly(methyl methacrylate) chains were then grafted from the CNC-macroalkoxyamine surface to give polymer-modified CNC [202].

2.4 Single-Electron Transfer Living Radical Polymerization (SET-LRP) of Cellulose

The last controlled polymerization method based on radical mechanism is SET-LRP in which dormant chains (or initiator) are activated via the outer-sphere electron transfer [203]. SET-LRP needs an initiating system that contains halide-type initiator (sulfonyl halides, haloacid esters, etc.), similar to those for ATRP, zero-valent copper, and appropriate ligand, like pentamethyldiethylenetriamine (PMDETA) or tris(2-dimethylaminoethyl)amine (Me_6TREN), in various solvents [198]. SET-LRP differs from ATRP regarding the low activation energy in an outer-sphere electron transfer mechanism for SET-LRP and also the rapid disproportionation of Cu^I with *N*-containing ligands in polar solvents [204]. Since CuX can disproportionate into Cu^0 and CuX_2 species in polar solvents in the presence of *N*-containing ligands [198], rapid living radical polymerization was observed in SET-LRP via the outer-sphere single-electron transfer mechanism. Therefore, Cu^I-mediated ATRP of *N*-isopropylacrylamide in polar solvent proceeded via Cu^0-mediated SET-LRP, and the reaction is not an ATRP [205]. The solvent effect is crucial because deactivating complex salt of Cu^{II} originates from the disproportionation of the Cu^I salt. The rate of which substantially depends on the solvent used [206]. Hence, polar solvents such as DMF, DMSO, and methanol are generally used in SET-LRP. The modifications of cellulose using SET-LRP are listed in Table 4.

2.5 Other Modification Methods of Cellulose with Polymers

While most of the cellulose-grafted polymers take place with one of the radical mechanism mentioned in previous sections, some of the modifications were reported in an unradical mechanism or a radical mechanism with unusual routes. Table 5 describes some of these reports regarding used methods and materials and obtained products.

Table 4 Polymer-grafted cellulosic materials prepared via SET-LRP method

Cellulose material	Initiator	Monomers	Catalyst	Reaction conditions	Ref.
Cellulose	-Br	AAm or DMAAm	CuCl/PMDETA	DMSO, 80 °C	[207]
CNCs	-Br	tBA, AA	CuBr/PMDETA	DMF, 75 °C	[131]
CNCs	-Br	NIPAm	CuBr/PMDETA	H_2O/MeOH, r.t.	[208]
CDA, CBA	-Br, -Cl	MMA, BuA, t-BuA	Cu^0/PMDETA	1,4-Dioxane, DMSO, 30, 60 °C	[209]
			Cu^0/Me_6TREN		
Softwood	-Br	DMAam	CuCl/PMDETA	DMSO, 80 °C	[129]
Cotton fiber	-Br	BMA, PETA	Cu^0/HMTA	DMF, 75 °C	[210]
EC	-Br	NIPAm	CuCl/Me_6TREN	THF/MeOH, 50 °C	[205]

See references to observe the abbreviations

Table 5 Polymer-grafted cellulosic materials obtained from unusual mechanisms

Cellulosic material	Modification material	Product	Method	Ref.
CNC	Isophorone diisocyanate (IPDI)	Polyurethane-CNC	(i) Modification of CNC with IPDI and (ii) polymerization with polyether alcohol	[211]
CNC	ε-Caprolactone	poly(ε-caprolactone)-grafted CNC	Ring-opening polymerization	[212]
CNC	*N*-Hydroxysuccinimide methacrylate (NHSMA), 2-isopropenyl-2-oxazoline (IPO), methyl methacrylate, styrene	Ps, PMMA, PIPOx, and PNHSMA-grafted CNC	UV-induced photopolymerization in the absence of any initiator	[213]
CNC	Acrylonitrile	Poly(propylene imine) (PPI)-grafted CNC	Michael addition of acrylonitrile onto amine-functionalized CNC	[214]
Cellulose	*N*,*N*′-Methylenebisacrylamide	Cellulose-grafted acrylamide copolymer	Without any radical initiator using microwave radiation in 1-butyl-3-methylimidazolium chloride ionic liquid	[215]
Cellulose	Isatoic anhydride (IA), 2-methyl-2-oxazoline (MOZ)	Cellulose-poly(2-methyl-2-oxazoline) composite	(i) Amination of cellulose with IA and (ii) modification of cellulose-IA with polyMOZ	[216]
CNFs	Ethylenediamine (EDA), polyethylenimine (PEI), bisphenol A epoxy resin	CNFs-PEI/epoxy nanocomposites	(i) Modification of CNFs with EDA, (ii) reaction of PEI with CNFs-EDA, and (iii) reaction of epoxy resin with product (ii)	[217]
CNFs	3-Methacryloxypropyltrimethoxysilane (MEMO), poly(lactic acid) (PLA)	CNF-PLA composite	(i) Modification of CNFs with MEMO and (ii) binding of PLA to CNFs-MEMO	[218]
CNFs	*L*-lactic acid	CNs-poly(LA)	(i) Modification of CNs with LA and (ii) polymerization of LA	[219]
CNFs	Maleic anhydride-grafted polystyrene-block-poly (ethylene-ran-butylene)-block-polystyrene (MA-SEBS)	CNF-grafted MA-SEBS	Reaction of CNFs with MA-SEBS via ring opening of maleic anhydride	[220]
Cellulose film	Polyurethane acrylate (PUA) prepolymers	Cellulose-PUA film	Reaction of cellulose film with PUA prepolymer with UV curing	[221]
MCC	Isobutyl vinyl ether (IBVE)	MCC-block-PIBVE	Ball milling of MCC and IBVE in vacuum	[222]

See references to observe the abbreviations

3 Cellulose Modification by Different Nanoparticles and Other Minerals

3.1 Nanoparticles

Metal nanoparticles have attracted more attention due to their various applications such as water purification, catalysis of chemical reactions, and hydrogen storage. Nanoparticles such as different metals, magnetic nanoparticle (iron oxides, cobalt-iron oxide, nickel, etc.), silica, and metal oxide tend to agglomerate to form stable and larger-size particles due to their high active surface area. In recent years, in order to prevent the agglomeration and to stabilize the nanoparticle structures, immobilization of metal nanoparticles on different kinds of substrates such as dendrimers, synthetic polymers, natural polymers, surfactants, and carbon nanotube-grafted polymers has received considerable interest. These synthesized nanocomposites have important applications in optics, electronic devices, catalysis, sensors, medical applications, etc. [223].

3.2 Modification of Cellulose Surface with Different Nanoparticles

Surface modification of cellulose with different nanoparticles led to producing of the modified nanocomposite with a wide range of applications. Here we will introduce and investigate the properties of these modified nanocomposites.

3.2.1 Palladium Nanoparticle

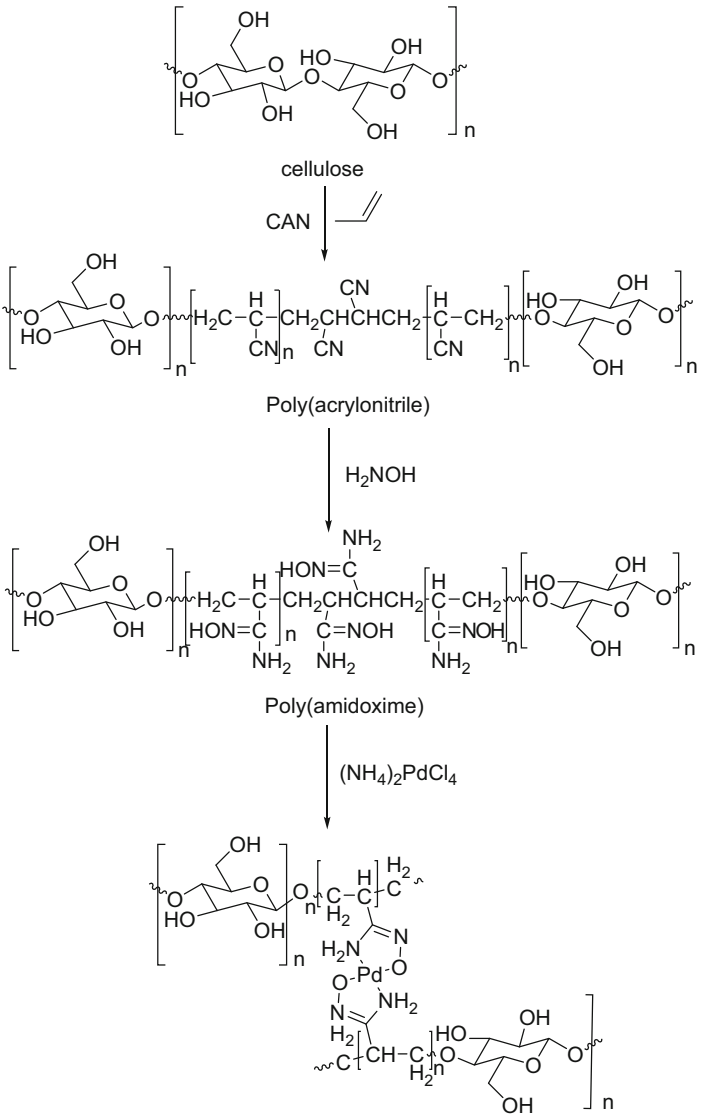
Palladium is one of the most efficient transition metals in catalysis field [224]. Recently, much attention has been paid to the palladium-based materials. Palladium nanoparticles have been investigated in a wide range of catalytic applications such as hydrogenations, oxidations, carbon-carbon bond formation, and electrochemical reactions in fuel cells [225]. However, these materials have different applications. For example, due to the tendency of palladium for adsorbing hydrogen, palladium nanoparticles are applied in hydrogen storage and sensing applications [226]. Due to the aggregation and precipitation of palladium metal in homogeneous palladium catalysts, they lose their catalytic activity. However, tedious workup procedures, loss of catalyst, and contamination of residual metals in the final product are the major drawbacks of these methods. Using heterogeneous palladium catalysts is the best choice to resolve these problems. Thus, it is possible by immobilizing palladium on suitable supports, which can be easily separated from the product without losing catalytic activity. Notably, chemical modification of the cellulose can be occurred by immobilization of transition metal onto the cellulose surface. In order to immobilize more metal on the cellulose surface, various polymers and linkers modify the cellulose surface.

Catalytic Activity

Transition metal catalysis can be catalyzed by 1,3-dipolar cycloaddition reaction, oxidation, direct arylation, and cross-coupling reactions. Palladium-catalyzed

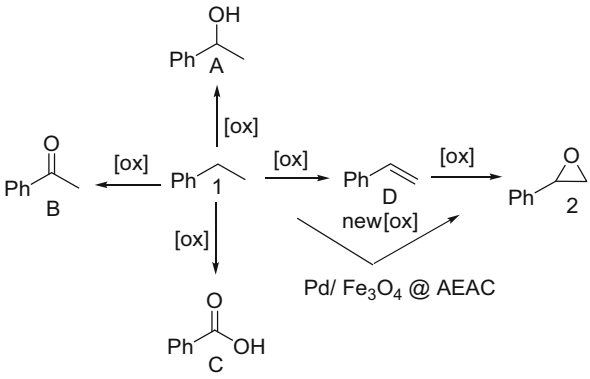
Suzuki, Sonogashira, and Heck couplings are all very important and powerful strategies for the formation of carbon-carbon bonds. There are many examples in this area; some of them will be presented below.

In 2017, a bio-waste corncob cellulose-supported poly(amidoxime) Pd(II) complex was synthesized by S.M. Sarkar and coworkers for the catalytic application in Mizoroki-Heck reaction (Scheme 10). The Pd(II) complex showed an excellent



Scheme 10 Synthesis of cellulose-supported poly(amidoxime) Pd(II) complex

Scheme 11 Oxidation reactions of ethylbenzene



catalytic activity toward the Mizoroki-Heck reaction of aryl halides and aryl diazonium tetrauoroborate salts with a variety of olefins under ambient reaction conditions with regeneration of the Pd(II) complex [227].

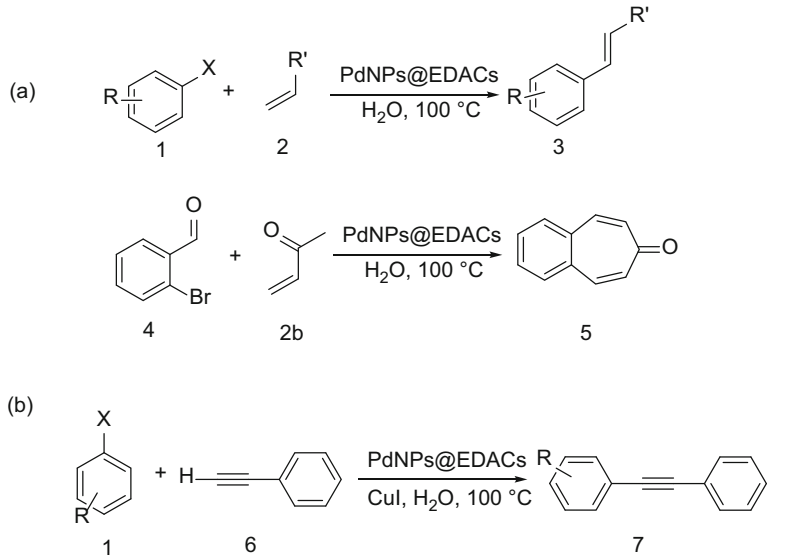
As can be seen in Scheme 11, Keshipour et al. have reported the oxidation of ethylbenzene to styrene oxide in the presence of cellulose-supported Pd magnetic nanoparticles. In this work, a new and efficient catalytic system involving Pd(0)/Fe_3O_4 nanoparticles (NPs) supported on *N*-(2-aminoethyl)acetamide-functionalized cellulose (AEAC) was synthesized and applied as a heterogeneous recoverable catalyst (Pd/Fe_3O_4NP@AEAC) with H_2O_2 as a green oxidant in the oxidation of ethylbenzene to styrene oxide [81].

As shown in Scheme 12, palladium nanoparticles supported on ethylenediamine-functionalized cellulose was synthesized in 2013 by Keshipour et al. and applied as a novel and efficient catalyst for the Heck and Sonogashira couplings in H_2O as a green solvent at 100 °C in a very low loading of Pd. After completion of the reaction, the catalyst could be easily recovered by simple filtration and reused for at least four cycles without significant loss of catalytic activity [97].

Also, this catalyst was used as an electrocatalyst for oxidation of hydrazine. In this work, cellulose was functionalized with ethylenediamine and then used as a support for the preparation of PdNPs immobilized on ethylenediamine cellulose (PdNPs-EDAC) which consisted of uniformly distributed palladium nanoparticles with the main average size of 4.7–6.9 nm. Finally, electrocatalytic activity of a PdNPs-EDAC has been investigated for the oxidation of hydrazine as an important model compound [100].

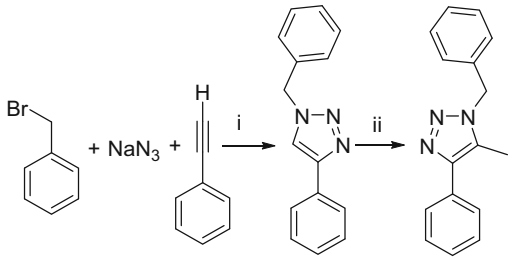
In 2013, Keshipour and coworkers have presented copper(I) and palladium nanoparticles supported on ethylenediamine-functionalized cellulose and suggested for it to be catalytically applicable to both 1,3-dipolar cycloaddition and direct arylation reactions (Scheme 13) [98].

Recently, this group has shown a new efficient catalyst for the green reduction of nitroaromatics (Scheme 14). The catalyst was obtained via modification of cellulose with N-doped graphene quantum dots and Pd nanoparticles. The new cellulose nanocomposite after characterization was applied as the catalyst in the reduction



Scheme 12 (**a**) Heck coupling reaction of styrene and methyl vinyl ketone with halobenzenes and (**b**) Sonogashira coupling of halobenzenes and phenylacetylene

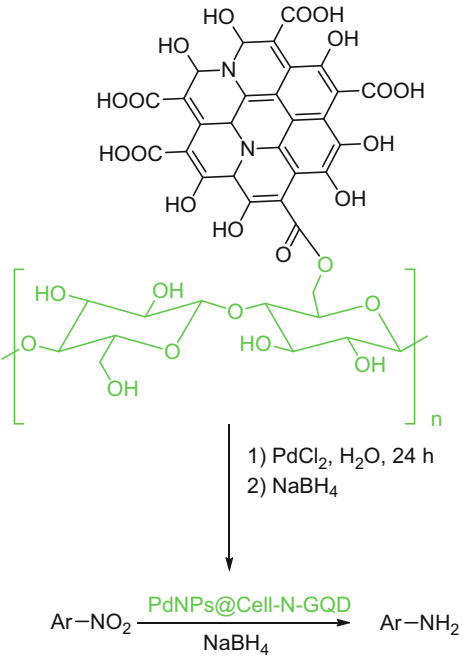
Scheme 13 Cu(I)/PdNPs@EDAC-catalyzed one-pot synthesis of triazoles



reaction of nitroaromatics using $NaBH_4$ at room temperature. Aromatic amines were obtained as the product of the reduction reaction over 2 h. This reaction has green reaction conditions such as mild reaction conditions, high yield, green solvent, and recyclable catalyst. In addition, the recovered catalyst is applicable in the reduction reaction six times without significant decrease in activity [123].

In 2017, a novel ferrocene tethered *N*-heterocyclic carbene-Pd complex anchored on cellulose has been synthesized in several steps by Salunkhe and coworkers. Then it is used as an efficient heterogeneous catalyst for synthesis of biaryls in Suzuki-Miyaura cross-coupling reaction. Some of the notable features of this procedure are good catalytic efficiency, high yields of products, easy separation, large-scale synthesis, and facile recyclability [228].

Scheme 14 Reduction of nitroaromatics with PdNPs@Cell-*N*-GQD



3.2.2 Silver Nanoparticle

Much attention has been paid to silver nanoparticles (AgNPs) due to their unique properties at the nanoscale size. These nanoparticles have several applications in optical, catalytic, magnetic, electrical, and antimicrobial devices. Immobilization of Ag onto polymer and biopolymer surfaces led to improve the properties and applicability of such polymers and biopolymers. As a result, bionanocomposites will be obtained [229]. Some of these applications will be presented as below.

Electrical Activity

Liu et al. in 2017 have developed an in situ polymerization of aniline monomer onto the porous-structured cellulose scaffolds, and then electrodeposition of Ag nanoparticles carried out on the obtained conductive composites. In this study, Ag nanoparticles were deposited homogeneously on the matrix of polyaniline (PANI)/cellulose gels which will increase the conductivity of composites. The conductivity of Ag containing PANI/cellulose nanocomposite gels was increased to 0.94 S C m^{-1}, which was higher than that of pure PANI/cellulose composites (3.45×10^{-2} S C m^{-1}). Thus, this synthesized conductive composite could be used as an electrode for the supercapacitors [230].

Sun and coworkers have presented a self-reporting aerogel toward stress-sensitive electricity (SSE) via combined routes of silver mirror reaction and ultrasonication. Sphere-like Ag nanoparticles (AgNPs) with a mean diameter of 74 nm were tightly immobilized in the cellulose nanofiber. The resulted Ag/CNF as a self-reporting

material for SSE not only possessed quick response and sensitivity but also easily recovered after 100th compressive cycles without plastic deformation or degradation in compressive strength. Consequently, Ag/CNF could play a viable role in self-reporting materials as a quick electric stress-responsive sensor [231].

Antibacterial Activity

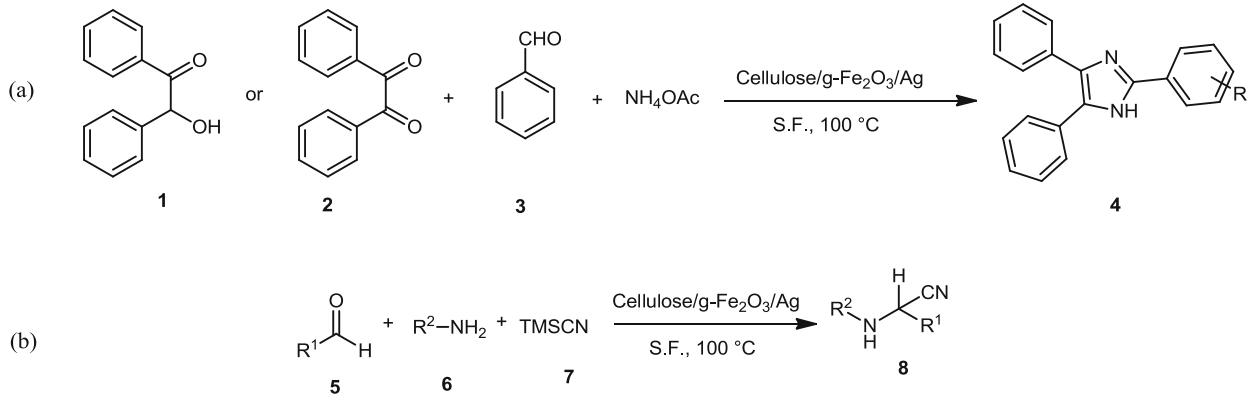
A porous hydrophobic Ag/Ag_2O@cellulose hybrid membrane was prepared by Zhang et al. in 2015. Cellulose is much more flexible, lighter, biodegradable, and ventilated in comparison with most of the existing water-strider-mimicking boats which are built from metals. In addition, the synthesized membrane has shown a water contact angle of 140°. Also, this hybrid membrane exhibited oil/water separation capacity, and it has strong antibacterial activity against *Escherichia coli* [232].

Huang and coworkers have synthesized an antibacterial cellulose/titania/chitosan hybrid material. Firstly, these hybrid materials were prepared by continuously depositing titania gel layer and chitosan layer on the cellulose microfibril bundles of filter paper. After that, silver ions adsorbed with the titania/chitosan composite film, followed by in situ reductions of the immobilized silver ions under UV irradiation. The finalized antibacterial cellulose/titania/chitosan/AgNP hybrid materials were obtained having the fibrous structure of the initial cellulose substance. These hybrid composites showed splendid antibacterial activities due to the intrinsic biocidal effect of titania composition, positively charged chitosan component, and high loading content of AgNPs with small size. Therefore, these AgNP-containing cellulose materials have antibacterial applications such as antibacterial wound dressing, antibacterial packaging, antibacterial adhesion, air/water purification, and so on [233].

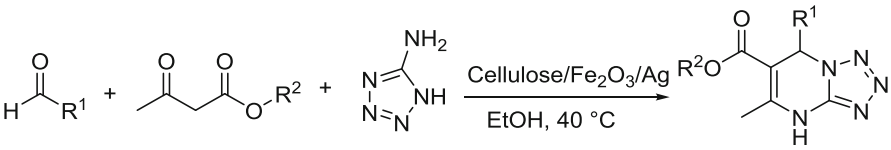
Vosmansk and coworkers have presented the three-step modification of the standard cellulose wound dressing. This method is cost-effective and environmentally benign and does not require the large and complicated device. The best outcome has been shown in the three-step modification of wound dressing including argon plasma treatment, chitosan impregnation, and AgCl precipitation. It also has antibacterial activity against *E. coli* and *S. epidermidis*. The surface of cellulose wound dressing was hydrophilic with the highest amounts of chitosan and AgCl in it. Chitosan was used here due to the antibacterial and healing promoting activity. The amount of adsorbed chitosan has positively affected on the amount of the AgCl in the surface, and as a result, AgCl and chitosan were responsible for the antibacterial effect of the wound dressing. It was found that the combination of chitosan and AgCl precipitation showed better antibacterial effect than each of them alone [234].

Catalytic Activity

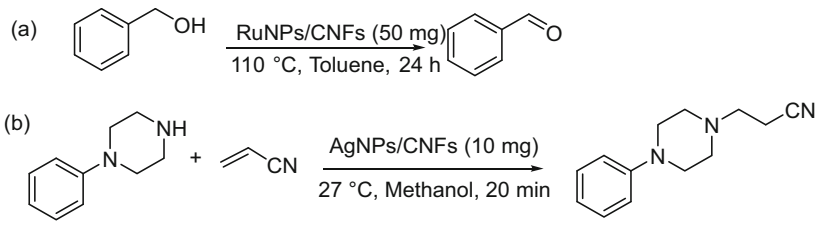
In 2016, Maleki and coworkers have synthesized a cellulose/γ-Fe_2O_3/Ag nanocomposite and applied as a catalyst for the synthesis of trisubstituted imidazoles and α-aminonitriles (Scheme 15). This method is simple and the yields of the products are very high in very short reaction time. The catalyst can be easily separated from the reaction mixture due to its remarkable magnetic properties, and it can be used for several times without considerable loss of catalytic activity. Meantime,



Scheme 15 (**a**) Synthesis of 2,4,5-trisubstituted-1*H*-imidazoles **4** and (**b**) synthesis of α-aminonitriles **8** using cellulose/γ-Fe_2O_3/Ag nanocatalyst under solvent-free conditions



Scheme 16 Synthesis of 5-methyl-7-aryl-4,7-dihydrotetrazolo[1,5-a]pyrimidine-6-carboxylic esters in the presence of magnetic cellulose/Ag bionanocomposite



Scheme 17 (**a**) RuNP/CNF-catalyzed oxidation of benzyl alcohol to benzaldehyde and (**b**) Ag/CNF-catalyzed *aza*-Michael reaction of 1-phenylpiperazine with acrylonitrile

antibacterial properties of the nanocomposite are investigated in this paper. For this purpose, *S. aureus* as the representative of gram-positive bacteria and *E. coli* as the representative of gram-negative bacteria are evaluated. As a result, it has antibacterial activity as well as catalytic application [235].

Also in 2017, for another time, this bionanocomposite catalyst was used by Maleki's group for green synthesis of tetrazolo[1,5-a]pyrimidines. This method has shown various advantages such as easy catalyst recycling, inexpensive catalyst, environmentally benign procedure, short reaction time, and high product yield (Scheme 16) [228].

Hussain et al. in 2014 have represented various methods to immobilize gold and silver nanoparticles on the surface of cellulose fibers. It this work, formation and immobilization of gold and silver nanoparticles occurred through boiling of the cellulose fibers in an alkaline solution of gold and silver salts. The synthesized thiol-modified cellulose fibers loaded with gold and silver nanoparticles were investigated for the catalytic reduction of 4-nitrophenol into 4-aminophenol [236].

Chung et al. have reported noble metal/functionalized cellulose nanofiber composites and investigated their catalytic activities in the aerobic oxidation of benzyl alcohol to benzaldehyde. These heterogeneous nanocomposites are highly efficient, stable, and reusable. In this work, simple reduction method has been used to synthesize MNPs supported on CNFs (RuNPs/CNFs and AgNPs/CNFs). As can be seen in Scheme 17, after characterization of the RuNPs/CNFs and AgNPs/CNFs, their catalytic activities were investigated for the oxidation of benzyl alcohol and *aza*-Michael reaction, respectively [237].

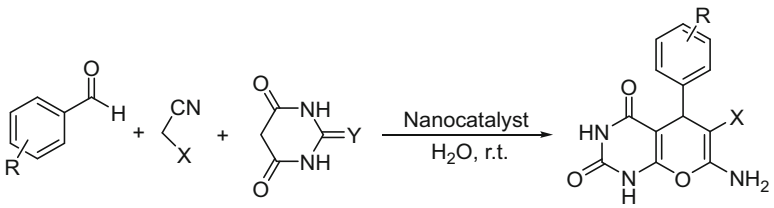
3.2.3 Iron Nanoparticle

Among all transition metals, iron is the most important one and the fourth most plentiful element in the Earth's crust. Iron nanoparticles can be prepared via several methods. Much attention has been paid to this nanoparticle due to their important applications such as treatment to many types of contamination; magnetic data storage and resonance imaging (MRI); medical and laboratory applications, using memory tape due to their magnetic properties; and catalyst applications.

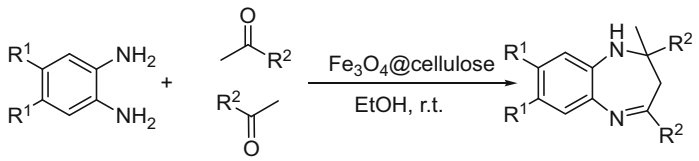
Catalytic Activity

A cellulose-based nanobiocomposite decorated with Fe_3O_4 nanoparticles has been reported by Maleki et al. in 2017 and used as an easily recoverable and reusable green nanocatalyst in the synthesis of pyrano[2,3-*d*]pyrimidine derivatives in water at room temperature (Scheme 18). In this study, two series of pyranopyrimidine and pyrazolopyranopyrimidine derivatives were synthesized by using the present cellulose-based nanocomposite. There were several advantages in these methods including reusability, high yield of the products, short reaction times, mild reaction conditions, and easy workup procedure [238].

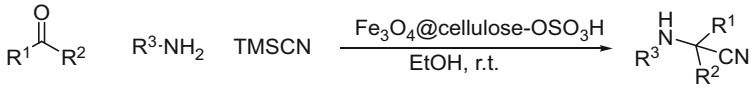
As can be seen in Scheme 19, in 2014, Maleki et al. presented a new cellulose-based nanocomposite with highly loaded Fe_3O_4 nanoparticles. Then, its catalytic activity was investigated in the condensation reaction between *o*-phenylenediamines and ketones to provide benzodiazepine derivatives in good to excellent yields under mild reaction conditions. A good correlation between the amounts of surface acid sites and the morphology of the catalyst and its catalytic activity was found. The nanocatalyst could be recycled and reused without significant loss of its catalytic activity [239].



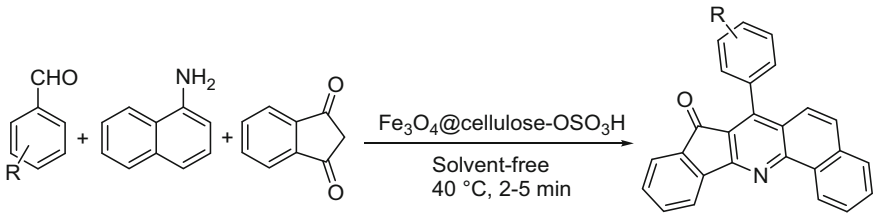
Scheme 18 Synthesis of pyrano[2,3-*d*]pyrimidine derivatives in the presence of the nanocatalyst



Scheme 19 Synthesis of 1,5-benzodiazepines in the presence of Fe_3O_4@cellulose nanocomposite



Scheme 20 MCSA-catalyzed Strecker reaction



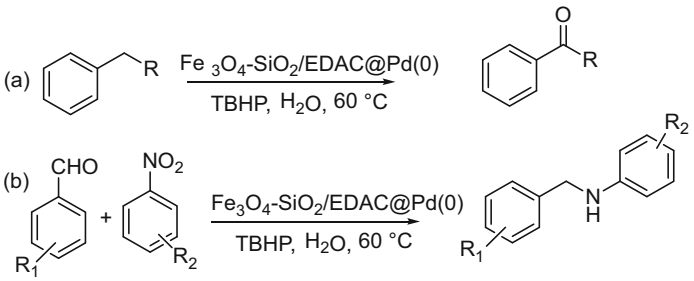
Scheme 21 MCSA-catalyzed synthesis of 7-aryl-8*H*-benzo[*h*]indeno[1,2-*b*]quinoline-8-ones

In 2014 Lu et al. reported a facile synthetic method for in situ immobilization of Au nanoparticles (NPs) on magnetic γ-Fe_2O_3@carboxylated cellulose nanospheres. Firstly, the γ-Fe_2O_3@cellulose NPs were synthesized via an ionic liquid-assisted coprecipitation process. After that, oxidation of cellulose occurred in the presence of TEMPO to produce carboxyl groups on the surface of magnetic nanoparticles (MNPs). Finally, by reducing of Au^{3+} by cellulose, AuNPs were dispersed onto the surface of magnetic γ-Fe_2O_3@carboxylated cellulose. The synthesized magnetic biopolymer-metal nanohybrids are used as a magnetic catalyst in the reduction reaction of 4-nitrophenol to 4-aminophenol [240].

In 2016, Maleki and coworkers have introduced a sulfonated magnetic cellulose-based nanocomposite [Fe_3O_4@cellulose-OSO_3H (MCSA)] and investigated its catalytic activity for the synthesis of α-aminonitriles via a one-pot three-component reaction of aldehydes or ketones, amines, and trimethylsilyl cyanide (TMSCN) in EtOH at room temperature (Scheme 20) [241].

In 2017, Maleki and coworkers in another study have applied above sulfonated magnetic cellulose-based nanocomposite as an efficient, inexpensive, and green catalyst for the one-pot three-component synthesis of 7-aryl-8*H*-benzo[*h*]indeno [1,2-*b*]quinoline-8-ones starting from 1,3-indanedione, aromatic aldehydes, and 1-naphthylamine under solvent-free conditions in high yields within short reaction times. The advantages of this nanobiostructure catalyst are easy separation by using an external magnet and reusability for several times (Scheme 21) [242].

Cellulose-magnetite nanocomposites were synthesized via the adsorption of magnetite onto the surfaces of functionalized nanocellulose, using different organic and inorganic acids such as acetic anhydride, succinic acid anhydride, chlorosulfonic acid, and $POCl_3$ by El-Nahas and coworkers in 2017. The properties of these functionalized nanocellulose derivatives and cellulose-magnetite nanocomposites were evaluated, and then the catalytic activity of the functionalized nanocellulose and cellulose-magnetite nanocomposites was investigated for the esterification



Scheme 22 (**a**) C–H bond oxidation and (**b**) reductive amination of aldehydes with nitroarenes in the presence of Fe_3O_4@SiO_2/EDAC-Pd(0)

of oleic acid with methanol for the production of methyl oleate (biodiesel). In this study, the sulfonated cellulose-magnetite nanocomposite (MSNC) showed the highest catalytic activity toward the esterification reaction (96%) due to the high dispersion of the Lewis acid sites which resulted from the impregnation of magnetite (0.98 wt%) in addition to the already presented Brönsted acid sites on the surface of the nanocellulose [243].

In 2013, a facile and novel methodology for the synthesis of palladium nanoparticles onto amine-functionalized inorganic/organic magnetic composite [Fe_3O_4@SiO_2/EDAC-Pd(0)] was reported (Scheme 22). The catalytic activity of the novel Fe_3O_4@SiO_2/EDAC-Pd(0) was investigated in the oxidation of benzylic C–H bond using TBHP and for the one-pot reductive amination of aldehydes with nitroarenes in the presence of molecular hydrogen. As a result, the catalyst has an excellent catalytic activity in both reactions and could be reused efficiently several times with high efficiency [244].

Antibacterial Activity

Glucose-reinforced Fe_3O_4@cellulose-mediated amino acid was developed by Rezayan et al., and this is the first report of applying magnetic cellulose nanocomposite as a support for bacteria capturing. In this study, two kinds of amino acid were applied as a linker to immobilize glucose on the surface of magnetic cellulose. It was found that using amino acids as a linker for glucose anchoring led to increase capturing efficiency for gram-positive bacteria as a sample pathogen. Also, this synthesized system was evaluated as a green biocompatible nanostructure for water treatment [245].

Wastewater Treatment

Liu and coworkers have reported ferric hydroxide-coated cellulose nanofibers ($Fe(OH)_3$@CNFs) and applied for the removal of phosphate from wastewater. This modified nanofiber has maximum sorption capacity of 142.86 mg/g which has higher adsorption capacity than many adsorbents reported in the literature. It was found that an increased solution ionic strength would increase the adsorption

capacity. Furthermore, the effect of PH conditions was investigated for determining a favorable adsorption performance of these nanofibers. The maximum adsorption capacity of $Fe(OH)_3$@CNFs was achieved at pH of 4.5. This study showed that ferric hydroxide-modified CNFs had a unique ability to remove phosphate from aqueous medium [246].

3.2.4 Zinc Oxide Nanoparticle

Due to nutritional properties, effective antimicrobial properties at low concentrations, high stability against high temperatures, nontoxicity, and good UV absorbance properties, zinc oxide has attracted much attention in food and pharmacy fields. Thus, the addition of ZnO NPs to the film packaging and its probable diffusion of the food products are not harmful to human health because these nanoparticles are used as nutrient agent [247]. Recently, the effective antimicrobial properties of ZnO NPs in active films have been reported for starch films against *Staphylococcus aureus* [248], polylactic acid-ZnO NP nanocomposite films against *Escherichia coli* and *Staphylococcus aureus* [249], chitosan-neem oil-based film against *E. coli* [250], and sodium alginate-gum acacia hydrogels versus *Pseudomonas aeruginosa* and *Bacillus cereus* [251]. Due to the high surface area of metal nanoparticles, they have superior antimicrobial properties [252].

Antimicrobial Activity

Ghanbarzadeh and coworkers have represented an active nanocomposite based on carboxymethyl cellulose-chitosan-oleic acid (CMC-CH-OL) incorporated with different concentrations (0.5–2 wt%) of zinc oxide nanoparticles (ZnO NPs) toward casting method. Then effects of ZnO NPs on the morphological, mechanical, thermal, physical, and antifungal properties of the films were investigated. Antifungal properties of these active nanocomposite films by disc diffusion test confirmed considerable antifungal rule against *Aspergillus niger*, especially in 2 wt% of CMC–CH–OL–ZnO which illustrated more than 40% fungal growth inhibition [253].

Rujiravanit and coworkers have reported that bacterial cellulose (BC) is a remarkable natural polymeric template to support the ZnO synthesized via solution plasma process (SPP). In addition, in SPP method, there was no need for a reducing agent. The ZnO/BC composites obtained via SPP had strong antibacterial activity against *E. coli* and *S. aureus*. Meantime, by increasing the ZnO content in the ZnO/BC composites, the antibacterial activity of the ZnO/BC composites will be increased. Notably, these composites might be applied in wastewater treatment but also in biomedical applications [254].

3.2.5 Cobalt Nanoparticle

Cobalt nanoparticles are a gray or black powder with spherical morphology. These nanoparticles have attracted much attention due to their magnetic properties. Due to these properties, they have been shown in imaging, sensors, catalyst, and many other areas.

Catalytic Activity

Ethylenediamine-functionalized nanocellulose complexed with cobalt(II) was reported by Shaabani and coworker in 2014 as a highly efficient heterogeneous catalyst for the room temperature aerobic oxidation of various types of primary and secondary benzylic alcohols into their corresponding aldehydes and ketones, respectively. Noteworthy, this catalyst was recovered and reused for five times with no significant loss of efficiency [122].

Magnetic *D*-penicillamine-functionalized cellulose as a new heterogeneous support for cobalt(II) was presented by Keshipour and coworker and applied in the green oxidation of ethylbenzene to acetophenone. The catalyst was obtained in three steps: first of all functionalization of cellulose with D-penicillamine occurred, after that deposition of Fe_3O_4 nanoparticles on cellulose-D-penicillamine, and finally, anchoring of Co(II) to the magnetic cellulose-D-penicillamine. The catalytic activity of composite was investigated for the oxidation of ethylbenzene to acetophenone in ethanol under reflux conditions using H_2O as a green oxidant. Also, the recovered catalyst could be used several times without significant loss of activity [80].

3.2.6 Titanium Dioxide Nanoparticle

Titanium dioxide (TiO_2) has attracted considerable attention as a semiconductor for photocatalysis activity because of its high stability, low cost, and safety toward both humans and the environment. TiO_2 nanoparticles have been used for resolving the drawbacks of traditional epoxy fillers such as rubber beads and glass and can be overcome by increasing the stiffness, strength, and toughness [255].

Gas Separation

Surface modification of TiO_2 nanoparticles with biodegradable nanocellulose and synthesis of novel polyimide/cellulose/TiO_2 membrane has been developed by Ahmadizadegan in 2017. In this paper, novel polyimide/cellulose/TiO_2 bionanocomposites (PI/BNCs) were synthesized by a simple and inexpensive ultrasonic irradiation method. In this study, PI was synthesized toward direct polycondensation reaction of novel monomer dianhydride with 4-(2-(4-aminophenyl)-1,1,1,3,3,3-hexafluoropropan-2-yl)benzenemine. The gas separation properties of PI membrane with three cellulose/TiO_2 concentrations (5, 10, and 15 wt%) are investigated for gas permeation. The titania weight percentage of the PI/BNC membranes was evaluated for the permeability of this membrane, and the results showed that increasing TiO_2 concentration increased the permeabilities of CO_2, H_2, CH_4, and N_2 [256].

Drug Delivery

Kessler and coworkers have investigated the potential drug delivery systems for dermal applications of cellulose nanofiber-titania nanocomposites. In this work, a new type of cellulose nanofiber-titania nanocomposites grafted with three different types of model drugs such as diclofenac sodium, D-penicillamine, and phosphomycin was successfully synthesized. One of the most important advantages of this work is the use of titania as a binding linker between cellulose nanofibers and a drug molecule, which provides a slow and controlled release. The drug release was

investigated in the presence of three drug molecules. It was shown that the quickest release was observed for the more soluble painkiller, slower one for the anti-inflammatory agent, and the longest release took place for the strongly chemisorbed antibiotic agent [257].

3.2.7 Silica (SiO_2) Nanoparticle

Silica particles have wide applications in industries related to the production of pigments, pharmaceuticals, ceramics, and catalysts [258]. Furthermore, silica-based adsorbent materials have industrial applications for the removal of heavy metals and lanthanides [259, 260]. Also, in the recent years, much attention has been paid to improve the adsorptive properties a variety of functional groups grafted on the surface of mesoporous silica.

Removal of Lanthanides from Aqueous Medium

Iftekhar and coworkers have successfully synthesized cellulose-based silica (CLx/SiO_2) nanocomposite and investigated for the removal of Eu(III), La(III), and Sc(III). In this paper, two different cellulose-based silica (CLx/SiO_2) nanocomposites were synthesized and characterized by several techniques. XRD and FTIR analyses have confirmed the presence of mixed phases of cellulose and SiO_2. In this study, CLN/SiO_2 nanocomposite could be explored as an appropriate adsorbent for Eu(III), La(III), and Sc(III) and can be exploited for the preconcentration of REEs from the diluted aqueous medium [261].

Nasir et al. have synthesized SiO_2-cellulose acetate nanofiber via electrospinning process and investigated the characteristic of nanofiber composites such as nanostructure, morphology, and surface property. SiO_2 in nanofiber is a key factor for controlling the spreading time of water droplet on the surface of nanofiber. It was found that the spreading time of water droplet on the surface of cellulose acetate nanofiber is much faster than SiO_2-cellulose acetate nanofiber surface. SiO_2-cellulose acetate might be used as lithium ion battery separator and water purificator [262].

3.2.8 Gold Nanoparticle

Gold nanoparticles (AuNPs) have been utilized for the several applications such as optoelectronics [263], sensing [264], biomedicine [265], bioimaging [266], and gene delivery [267]. In addition, the catalytic activity of AuNPs is investigated for various chemical reactions such as the CO oxidation, C–C coupling reaction, aerobic oxidation of alcohols, and reduction reaction via transfer hydrogenation [268–270]. However, due to the large active surface areas, AuNPs are unstable and tend to irreversibly aggregate in solution. Therefore, catalytic activity will be reduced. The most effective way to resolve this drawback is immobilization of AuNPs on polymeric supports or inorganic material.

Catalytic Activity

TEMPO-oxidized bacterial cellulose nanofiber-supported gold nanoparticles have been reported by Chen and coworkers in 2016. In this work, the nanohybrid was successfully prepared by deposition of gold nanoparticles (AuNPs) onto the

surface of TEMPO-oxidized bacterial cellulose nanofibers (TOBCNs). The prepared AuNP/TOBCN nanohybrids were characterized by UV-vis spectral analysis, XRD, TEM, and HRTEM, and their catalytic activity for the reduction of 4-nitrophenol (4-NP) to 4-aminophenol (4-AP) was estimated by UV-vis spectrometry [271].

Huang and coworkers have shown the deposition of gold nanoparticles on titania gel film pre-coated cellulose nanofibers of filter paper. In this work, the catalytic activities of finalized bulk cellulose-based membranes were investigated for the reduction of 4-nitrophenol to 4-aminophenol through a facile filtration process [272].

3.2.9 Metal-Organic Frameworks

Metal-organic frameworks (MOFs) have been widely utilized for gas adsorption and separation [273], catalysis [274], sensors [275], drug delivery [276], humidity measurement [277], and nonlinear optics [278] due to their high porosity, high surface areas, versatile synthesis conditions, and unique properties [279]. These crystalline porous materials consist of metal ions or clusters and metal-ligand coordination bonds.

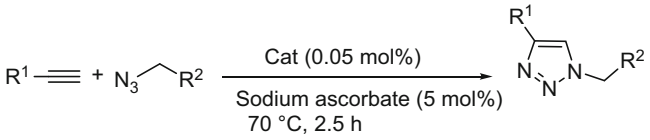
Gas Adsorption Activity

Shunxi Song and coworkers have prepared cellulose paper@MOF-5 composites with gas adsorption capacity. The synthesized cellulose paper@MOF composites were characterized by XRD, ATR-FTIR, SEM, and nitrogen adsorption analysis. In this study, cellulose paper@MOF-5 composite materials were prepared via in situ deposition of MOF-5 onto precipitated calcium carbonate (PCC)-filled cellulose paper. Hydrogen bonding between cellulose fibers decreased due to the presence of PCC fillers in the cellulose paper. Therefore, hydroxyl groups on the cellulose surface will be available for reacting with the organic ligand, i.e., 1,4-benzenedicarboxylic acid (BDC) in the MOF-5 formation process. The synthesized cellulose paper@MOF-5 composite materials had zeolite-like frameworks with high specific surface areas. Gas adsorption activity of this composite was investigated, and it was found that prepared paper@MOF-5 composites showed a high nitrogen gas adsorption capacity and could have great potential to adsorb or store gaseous products such as H_2, CO_2, CH_4, etc. [280].

3.2.10 Copper Nanoparticle

Copper is one of the most widely used materials in the world. The applications of copper (Cu) and Cu-based nanoparticles have attracted a great deal of interest in recent years, especially in the field of catalysis.

Sarkar and coworkers have reported a waste corncob cellulose-supported poly (hydroxamic acid) Cu(II) complex and applied their catalytic activity in the Huisgen 1,3-dipolar cycloaddition reaction using sodium ascorbate under mild reaction conditions (Scheme 23). In this study, waste materials have been used as a source of catalytic support. This resulted catalyst is recyclable, environment-friendly, and cost-effective bio-heterogeneous catalyst in chemical synthesis. Therefore, waste materials like corncob can be utilized as a heterogeneous solid support for metal-catalyzed chemical transformation reactions to ensure maximum use of our limited wealth [281].



Scheme 23 Huisgen cycloaddition reaction of azides and alkynes

4 Conclusion

Cellulose was found as a susceptible material for various modification reactions. Loading of various organic materials such as esters, ethers, silanes, halogens, amines, carbomates, polymers, and heterocycles on cellulose was reported. High activity of hydroxyl groups of cellulose makes the polymer as an active compound in the modification reactions. Also, cellulose can be modified with inorganic materials for the preparation of special compound with unique properties. While the cellulose reactions were investigated widely, the publications about cellulose modification are increasing that shows the high importance of cellulose-based materials in modern chemistry.

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Synthesis and Properties of Hydrogels Prepared by Various Polymerization Reaction Systems

16

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Contents

Abstract

Among all biomass, cellulose is the most abundant renewable polysaccharide in nature, accounting for approximately 40% of the lignocellulosic biomass. The ability of cellulose to absorb enormous amounts of water has prompted the large

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use of cellulose in preparation of various hydrogels. Cellulose-based hydrogels are generally synthesized by two steps, (i) solubilization of cellulose fibers or powder and (ii) physical and/or chemical cross-linking, in order to obtain a three-dimensional network of hydrophilic polymer chains. The physical synthesizing method includes ionic interaction, hydrophobic interaction, and hydrogen bond formation, whereas the chemically cross-linked hydrogel preparation involves different polymerization techniques such as chain-growth polymerization, irradiation polymerization, and step-growth polymerization. Further, another technique such as bulk polymerization is also used to form gels mainly using lactic acid as monomer. Indeed, the high density of free hydroxyl groups present in the cellulose structure permits them to undergo functionalization/chemical modification, which allows producing cellulose derivatives. The properties of cellulosic hydrogels change based on the different environmental stimuli. The external stimulus includes pH, temperature, light, electric or magnetic field, mechanical stress, etc. The responses of the hydrogel based on the exposure to different stimuli are discussed in this chapter. However, the cellulose hydrogels basically have good biocompatibility and non-toxicity combined with relevant mechanical properties. They showed highest absorption capacity, the swelling/deswelling behavior, and its rate depends on various factors such as particle size, porosity, solvent concentration, cross-linking density, etc. The swell behavior is addressed using various kinetic models such as Fickian, non-Fickian, and Flory. Further, biodegradation, mechanical, and rheological properties variation with respect to cross-linking density and other parameters (shape, pore size, reinforcement, etc.) and stimuli are considered and discussed.

Keywords
Polymerization · Hydrogel · Cross-linking · Properties

1 Introduction

Hydrogels are polymer networks that take in and keep huge quantities of water [1]. The characterizations of many kinds of hydrogels are prepared from different types of cellulose, alone or mixed with its derivatives, such as lignin, chitin, or polyvinyl alcohol [2, 3]. The cellulose-based hydrogel is generally prepared by two steps, (i) solubilization of cellulose fibers or powder and (ii) physical and/or chemical cross-linking, in order to obtain a three-dimensional network of hydrophilic polymer chains [4].

Hydrogels are held together by either physical interactions (chain entanglements, van der Waals forces, hydrogen bonds, crystallite associations, and/or ionic interactions) or chemical cross-links (covalent bonding) [5]. In case of physical cross-linking, the hydroxyl groups in cellulose can easily form hydrogen bonding network. Generally, it is very difficult to dissolve the cellulose in common solvents due to its highly extended hydrogen-bonded structure [6]. However, solvents such as *N*-methylmorpholine-*N*-oxide (NMMO), ionic liquids (ILs), and alkali/urea (or thiourea) are used to dissolve cellulose for the preparation of hydrogels. In

case of chemical cross-linking, the covalent bond formation takes place, depending on the cellulose derivatives, and a number of cross-linking agents and catalysts are used to form hydrogels. Epichlorohydrin, aldehydes, aldehyde-based reagents, anhydrides, urea derivatives, carbodiimides, multifunctional carboxylic acids, difunctional molecules [7], and cellulose/PVA are the most widely used cross-linkers for the preparation of cellulose hydrogels [8].

Several hydrogels are prepared by various researchers, and those cellulose-based hydrogels are commonly prepared using physical and cross-linking methods. The cellulose hydrogels based on its derivatives include methyl cellulose (MC), hydroxypropyl cellulose (HPC), hydroxypropylmethyl cellulose (HPMC), carboxymethylcellulose (CMC), ferrocene-cellulose (FC), and cyclodextrin-cellulose (CC), which are obtained by both physical and chemical cross-linking approaches [5].

The cross-linked hydrogels possess tridimensional and flexible structure, able to swell when they are immersed in aqueous solutions. Indeed, chemical or physical cross-linking avoids their solubilization, since water can penetrate through the network without breaking the strong interactions that bind the polymer chains together. Some hydrogels can also change their own volume in response to external stimuli such as solvents, temperature, pH, ionic force, electric field, light irradiation, and salt concentration. Because of these peculiar features, most of hydrogels are used in many applications such as tissue engineering, wound healing, drug delivery, hygiene, superabsorbent, biosensors, agriculture, etc. Furthermore, hydrogel properties such as swelling/deswelling, mechanical, rheological, biocompatibility, cytotoxicity, and biodegradability are tuned based on the requirement and particular application. Thus, this chapter focused on detail discussion on the preparation of cellulose and its derivation-based hydrogels (i.e., different physical and chemical cross-linking techniques). Further, the properties of the hydrogels and its response to environmental stimuli are discussed.

2 Preparation Methods of Cellulose-Based Hydrogels

Hydrogels can be prepared by different methods depending on the designed structure and the preferred application. General method of hydrogel formation is depicted in schematic representation, Fig. 1.

2.1 Physical Cross-Linking

Physically cross-linking is of great interest in the current era due to the absence of cross-linking agents and relative ease of production. The physical hydrogels (also called self-assembling hydrogels) are formed when macromolecules self-assemble through non-covalent, secondary molecular interactions such as hydrophobic, electrostatic, and H-bonding. In physically cross-linked gels, dissolution is prevented by physical interactions, which exist between different polymer chains (Fig. 2) [9]. All of these interactions are reversible and can be disrupted by changes in physical conditions or application of stress [10].

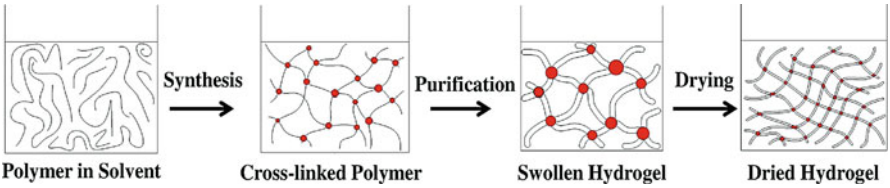
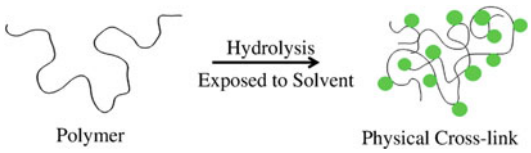


Fig. 1 Schematic representation of the steps involved in preparation of a hydrogel

Fig. 2 Representation of physical cross-linking of hydrogel



2.1.1 Cross-Linking by Hydrophobic Interaction

Hydrogels formed via hydrophobic interactions are mainly prepared by copolymerization of a hydrophilic monomer with a small amount of a hydrophobic comonomer, most typically by a free-radical mechanism [11]. Hydrophobic interactions are relatively stronger than other weak intermolecular forces (i.e., van der Waals interactions or hydrogen bonds). The strength of hydrophobic interactions depends on several factors which include temperature, number of carbon atoms on the hydrophobes, and shape of the hydrophobes. To create strong hydrophobic interactions between the hydrophilic polymer chains, a higher number of carbon-based hydrophobic polymer are utilized. In particular, the temperature has a remarkable effect on the hydrophobic interactions between hydrophobic polymer segments and the hydrophilic interactions between hydrophilic polymer segments and water molecules. The most abundant alkylated cellulose derivatives are methyl, ethyl, hydroxyethyl, and hydroxypropyl methyl cellulose. When solutions of these polymers are heated above certain temperatures, depending on the level of cellulose alkylation, hydrogels are obtained. The hydrophobic interaction occurs between the alkylated hydroxyl groups, and at low temperature, cellulose chains are hydrated, whereas at high temperature, water is repelled from the chains, and the alkylated hydroxyl groups interact with one another to form hydrogel [12].

2.1.2 Cross-Linking by Ionic Interactions

Ionic polymers can be cross-linked by the addition of di- or trivalent counterions. This method underlies the principle of gelling a polyelectrolyte solution (e.g., Na + alginate-) with a multivalent ion of opposite charges (e.g., Ca_{2+} + $2Cl^{-}$) [11]; i.e., simple ion exchange mechanism occurs to form hydrogels. Alginate is a well-known example of a polymer that can be cross-linked by ionic interactions. It is a polysaccharide with mannuronic and glucuronic acid residues and can be cross-linked by calcium ions [13]. Martínez-Ruvalcaba et al. developed ionically cross-linked two natural polyelectrolytes, chitosan and xanthan; since chitosan is a cationic

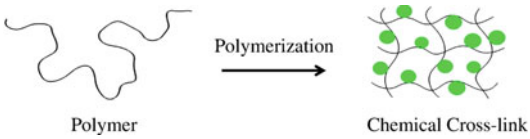


Fig. 3 Representation of chemical cross-linking of hydrogel

polyelectrolyte polymer with ionizable amine group anions, xanthan was employed as ionic cross-linkers to form hydrogel. The cross-linking are usually performed at room temperature and physiological pH; thus, they are particularly attractive in wound healing, drug delivery, and tissue engineering applications [14].

2.1.3 Cross-Linking by Hydrogen Bonds

Cellulose contains many hydroxyl groups which can form hydrogen bonding network. Hydrogen bonding interaction occurs between a pair of other atoms having a high electron affinity. Several gels were prepared through strong H-bonding interactions between highly hydroxyl functionalized chains. The presence of two functional groups produces hydrogen bonding with water to form gel structure. Hydrogels extended by this technique are influenced by various factors like polymer concentration, molar ratio of each polymer, type of solvent, solution temperature, and the degree of association of polymer functionalities [13, 15]. When polymer concentration is higher, gels become more and more organized and stable due to the higher degree of entanglements and hydrogen bonding interactions [16]. The hydrogen bond formation happens only when the carboxylic acid groups are protonated. However, hydrogen-bonded networks would be diluted and dispersed over a few hours owing to the influx of water [17].

2.2 Chemical Cross-Linking

In chemically cross-linked gels, covalent bonds are present between different polymer chains. Usually chemical modifications are performed to produce cellulose derivatives either by esterification or etherification [18]. Chemical cross-linking is a highly versatile method to create hydrogels with good mechanical stability. However, the cross-linking agents used are often toxic compounds, which will be extracted from the gels before they are utilized (Fig. 3) [9].

2.2.1 Chain-Growth Polymerization

Chemically cross-linked hydrogels are produced by chain-growth polymerization which includes free-radical polymerization; the process includes three steps, viz., initiation, propagation, and termination. Most commonly the hydrogels are synthesized by free-radical chain polymerizations of hydrophilic monomers containing a carbon double bond. The free-radical polymerization begins with initiator species, which produces active radical centers. The free radicals are produced by homolytic dissociation of weak bonds or by redox reactions. Once the active sites are produced, they rapidly propagate through the carbon double bonds of monomer, to form

polymer chains. The generation of active sites depends on the type of monomer and solvent and the reaction condition employed. In addition they are also based on the initiator heat (thermal initiators), light (photoinitiators), γ radiation, or electron beam. Chain termination occurs when the propagating radicals react by combination, disproportionation, and transfer [19, 20]. When hydrogels are synthesized using chain-growth polymerization, they create more heterogeneous network structure. The formation of hydrogel occurs by rapid propagation of active sites through monomers that contain multiple carbon-carbon double bonds [21]. These hydrogels would have high-molecular-weight kinetic chain, and they serve as cross-linking points. Due to the random nature of radical propagation and termination in chain-growth polymerization, cross-link functionality or the number of arms per cross-linking point is not static. The hydrogel formation occurs, once the network reaches the critical gelation point. This method of hydrogel preparation can be expressed in solution, suspension, and photopolymerization. The process is versatile and much employed to produce hydrogels in a variety of structures.

Solution Polymerization

In solution polymerization, the monomer, the initiator, and the resulting polymer are all soluble in the solvent or solvent blend. The solution polymerization usually starts with high concentration of monomer and minimum proportion of catalyst, initiator, and solvent. As the reaction proceeds, more solvent is added to regulate the viscosity, and additional catalyst/initiator is added to adjust the reaction rate. Among the homogeneous polymerizations, the solution polymerization is preferred due to better control of the heat of polymerization, lower cost, and ease of synthesis. Most of the cellulose-based superabsorbent hydrogels are produced in this way; Sannino et al. developed hydroxyethylcellulose (HEC) and carboxymethylcellulose sodium salt hydrogels using solution polymerization technique [22–25]. Author utilized different cross-linking agents and catalyst with a common solvent (water). Suo et al. developed cellulose-based superabsorbent polymer, i.e., carboxymethylcellulose-graft-poly(acrylic acid-co-acrylamide); their study adapted free-radical grafting solution polymerization of acrylic acid (AA) and acrylamide (AM) monomers onto carboxymethylcellulose (CMC) in the presence of *N,N′*-methylenebisacrylamide as a cross-linker and potassium persulfate/sodium metabisulfite as an initiator [26]. Researchers developed hydroxypropyl cellulose (HPC) hydrogels by free-radical polymerization in water; in their process the reaction was initiated by oxidant, and polyacids were grafted and interpenetrated with HPC [27–30]; and their report revealed that the prepared hydrogels were temperature responsive and pH responsive. This type of polymerization was used extensively because of high polymerization rate; in addition the reaction occurs in an aqueous medium, which is safe and harmless. Further, this process adds up an advantage over other cross-linking methods since it is performed at room temperature.

Suspension Polymerization

Suspension polymerization (wherein monomer-forming droplets, with the initiator in them, are completely insoluble and suspended in a solution) is the most common technique for the production of a variety of hydrogel networks by reacting

hydrophilic monomers with multifunctional cross-linkers and initiators. In the case of suspension polymerization, monomers and initiator are dispersed in the organic phase. In other words, the reaction mass is dispersed as minute droplets in a continuous aqueous phase; each droplet acts as tiny bulk reactors. Heat transfer occurs from the droplets to the water having large heat capacity and low viscosity. Thereby the cooling jackets are used to facilitate heat removal, and agitators are used along with suspending agents in the aqueous phase in order to maintain a specific droplet size and dispersion. The hydrogel properties developed through suspension polymerization depend on the viscosity of the monomer solution, agitation speed, rotor design, and dispersant type [31, 32]. The suspension gelation method (microcapsule templating method) is described to prepare macroporous polymeric hydrogels [33]. An aqueous suspension is formed by dispersing the microcapsules as a pore template (porogen) into a pre-gel aqueous solution containing monomers and cross-linking monomers. Then, the composite hydrogel containing distributed microcapsules are prepared by copolymerizing the pre-gel aqueous solution [34].

Photopolymerization

Photopolymerization is one of the important processes that enable in situ formation of cross-linked networks. Photopolymerizations are initiated by light and both the initiating species, usually induced by ultraviolet (100–400 nm), visible (400–700 nm), or infrared (780–20,000 nm) radiation. This process converts a liquid monomer or macromer to a hydrogel by free-radical polymerization [35]. Visible or UV light interacts with light-sensitive compounds, creates free radicals, and initiates polymerization to form cross-linked hydrogels [36]. Three major classes of photo-initiation depend on the mechanism involved in photolysis, which include radical photopolymerization through photo-cleavage, hydrogen abstraction, and cationic photopolymerization [36–38]. Many researchers have shown interest in utilizing the photo-initiated polymerization; for example, Reeves et al. developed carboxymethylcellulose (CMC) hydrogels using ultraviolet light as initiator [39], and Mann et al. developed a tissue-engineered hydrogel scaffold through photopolymerization of PEG derivatives with proteolytically degradable peptides [40]. The photopolymerized hydrogel systems can afford better temporal control over the gelation process. The alginate-based hydrogels were cross-linked by photo-irradiation; the rate of cross-linking was controlled by the exposure to ultraviolet (UV) light and physiological conditions [41]. Many researchers are interested in utilizing the photo-initiated polymerization of PEG-based macromolecular monomers to produce hydrogels as cell delivery vehicles for tissue regeneration. A comprehensively studied PEG hydrogel system occupied ultraviolet irradiation to generate radicals from specific photoinitiators, which will further react with the active end group on tailored PEG to form a covalent cross-linked bond. In addition to PEG, alginate, chitosan, hyaluronic acid, and chondroitin sulfate were also methacrylated, and the hydrogels were synthesized by photopolymerization [13].

2.2.2 Irradiation Polymerization

Radiation polymerization technique is an emerging technique to synthesize cellulose-based hydrogels. High energy radiations such as gamma rays and

electron beam are used to polymerize unsaturated substances [42, 43]. Water-soluble polymers could be transformed into hydrogels using high energy radiation. Ionizing radiations, such as electron beam and γ-rays, have high energy as much as necessary to ionize simple molecules either in air or water. During irradiation of a polymer solution, many reactive sites are generated alongside the polymer strands. After that, the combination of these radicals leads to formation of a large number of cross-links [13]. Electron-beam radiation (ionizing radiation) initiates the cross-linking and produces pure, sterile, and residue-free hydrogels. Unlike conventional chemical cross-linking methods, this method does not require the addition of catalysts or any other additives to modify the material [9]. Using this method, the degree of cross-linking and the pore size of hydrogels, which strongly determine the extent of swelling, can be easily controlled by varying the irradiation dose [44, 45]. Further, the use of toxic chemicals is completely eliminated in this method; hence, the poly-gels produced are free of toxic elements.

Frediani et al. adapted the microwave radiation to induce cross-linking; his study reported that the synthesized product possessed faster swelling and shrinking kinetics in comparison to the hydrogels prepared by conventional methods [46]. Fei et al. developed radiation cross-linked poly (ε-caprolactone) in supercooled state, and the product has shown high heat stability at a low dose of irradiation (30 kGy) [47–49]. Reeves et al. prepared CMC-methacrylate gels and CMC-methacrylate/PEG-DM copolymer gels using photoinduced free-radical cross-linking [39]. Liu et al. have also reported the preparation methodology of carboxymethylcellulose (CMC) hydrogels under γ-irradiation [50]. The concentration of free radicals in the system, determined by the dose rate, is an important factor for influencing the gel formation [51]. Considerably higher gel fraction occurs with the radiation dose. However, the product attained through radiation mechanism undergoes faster rate of degradation than the radiation of cross-linking.

2.2.3 Step-Growth Polymerization

Step-growth polymerization involves a reaction between dissimilar chemical groups which are part of the monomer molecules and forms a new bond (covalent bond) between the two functional groups. In this technique, the molecular weight of the polymer chain builds up slowly to form the polymer, i.e., only one reaction mechanism occurs in this method. The distinct initiation, propagation, and termination steps of chain-growth polymerization are meaningless in step-growth polymerization [52]. And more, the homogenous hydrogels are usually prepared via step-growth polymerization as they are formed by reacting at least two multifunctional monomers with mutually reactive groups; each monomer with defined functionality serves as a cross-linking point. Two cross-linking mechanisms form different hydrogel network structures; the variation on monomer molecular weight or concentration may have differential effect on hydrogel formation. Four-arm PEG functionalized with cycloctyne was reacted with azide difunctionalized polypeptides via strain-promoted alkyne-azide cycloaddition (SPAAC) reaction to form a hydrogel network via step-growth mechanism [53].

3 Environmental Stimuli

Macromolecular networks present in hydrogels absorb and release water solutions in a reversible manner; the response depends on specific environmental stimuli [54]. External stimuli include pH, temperature, light, magnetic field, and mechanical force [55–59]. The potential response to these stimuli also involves changes in shape, volume, phase, and optical properties. The stimuli-responsive volume change of the gels is a result of many factors such as the type of monomers, hydrophilic-hydrophobic balance, cross-link density, osmotic pressure, conformation of chemical groups, etc. (Fig. 4).

3.1 pH Responsive

pH-sensitive hydrogels consist of gel structure which varies with a change in pH values. The pH-sensitive hydrogels expand or contract depending upon the pH of the solutions. The cellulose-based gels are responsive to pH changes of the external solution. Appropriate pH and ionic strength generates electrostatic repulsive force results in swelling or deswelling of the hydrogel [60]. pH-responsive hydrogels could offer desirable physical and chemical properties at specific pH ranges. The acidic groups deprotonate at high pH, while the basic groups protonate at low pH. The association, dissociation, and binding of various ions to polymer chains cause hydrogel swelling in an aqueous solution [12]. The swelling capacity is directly related to both osmotic pressure and electrostatic repulsion according to the level of dissociation [61].

Polysaccharides usually respond to pH stimuli, which make them attractive for sustained drug release application [62]. In general, the size of the gel will respond to environment pH as well as salt concentration. Thus, an equilibrium model was established by Moore's group to predict the swelling/deswelling behavior of hydrogels in different pH solutions [63]. The effects of different hydrogels and solution conditions on the degree and rate of swelling/deswelling were investigated by many authors; they found that the higher the concentration and buffer diffusivity, the faster the kinetic [12].

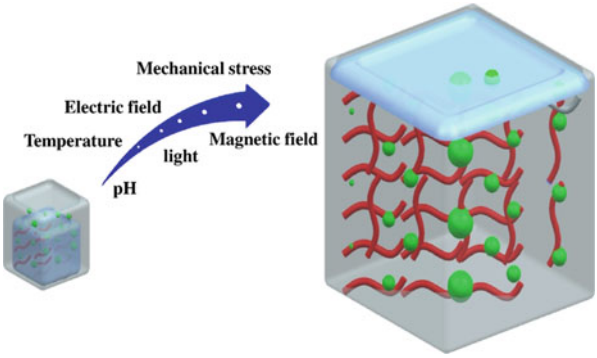


Fig. 4 Stimuli-responsive swelling of hydrogels

3.2 Temperature Responsive

The temperature is one of the important reaction parameters determining the grafting kinetics [64]. Temperature-sensitive hydrogels are also called as thermo-gels [65, 66]. These stimuli-sensitive hydrogels show changes in their swelling behavior of the network structure according to the external environments. The thermally induced abrupt change in the solubility is controlled by the Gibbs free energy of mixing [67].As most widely reported, thermally induced gelation is based on the equilibrium between hydrophobic and hydrophilic interactions [12]. There are many polymers belonging to the family of thermo-responsive polymer, systems mainly characterized by the presence of hydrophobic groups, such as methyl, ethyl, and propyl groups, which are used in the synthesis of hydrogels. These hydrogels are classified into positive thermosensitive, negative thermosensitive, and thermally irreversible hydrogels.

When the cellulose derivative polymer has positive thermo-sensitivity of swelling, they will be miscible at upper critical solution temperature (UCST), below which the polymer will be immiscible [45]. In case of negative thermo-sensitivity, the solubility of the hydrogels decreases at a temperature above lower critical solution temperature (LCST). In other words, the hydrogel starts to shrink when the temperature rises beyond the LCST because of the interpolymer chain association through hydrophobic interactions [68].

The other category is irreversible hydrogels; the non-covalent cross-linking in the hydrogels has the tendency to undergo sol-gel phase transition instead of swelling and shrinking transitions. Such hydrogels exhibit inverse temperature-dependent sol-gel behavior; they become sol as the temperature increases [64].

3.3 Light Responsive

Light-responsive materials have the ability to respond to stimuli triggered by the exposition to light sources such as UV, Vis, or infrared [69]. Light is a particularly interesting stimulus to manipulate the properties of a hydrogel, as it is a remote stimulus that is easily controlled. Common light-responsive materials are synthesized by the addition of photosensitive groups. Those gels undergo reversible photomechanical changes upon exposure to UV, visible, or IR light. Upon irradiation to ultraviolet light, the gels tend to deswell, while the reversal process occurs when exposed to visible/IR light [70]. Photoinduced self-healing polymers can mimic the biological systems in which damage triggers a self-healing response. These materials are used to repair fiber fracture, delamination, or propagation of micro-cracks of polymeric components used in a variety of applications, extending the functional life and safety of the polymeric components. The light-responsive hydrogels render higher advantages over others, as they could be instantly and accurately imposed. Also, the capacity for instantaneous delivery of the sol-gel stimulus renders light-responsive polymers potentially applicable for the development of optical switches, display units, and ophthalmic drug delivery systems [58, 71]. Further, various light-

sensitive drug delivery systems are used in photoresponsive prodrugs and photoresponsive drug carriers in diverse form including vesicles [70].

3.4 Electro-Responsive

Electric field-responsive hydrogels are polymers that swell, shrink, or bend in response to an applied electric field. They are usually made of polyanions, polycations, or amphoteric polyelectrolytes [72]. Under the influence of an electric field, electric-sensitive hydrogels deswell or bend, depending on their shape and their position relative to the electrodes. The extent of deswelling depends on the amount of charge transported through the gel, rather than on the applied voltage. When the electric field is removed, the hydrogel absorbs the solution and swells [73, 74]. The electrical response of polyelectrolyte hydrogels is influenced by many parameters, such as the shape and the orientation of the gel, its composition (charge density, nature, and hydrophobicity of cross-links, monomers, and pendant groups), the nature of the aqueous conducting medium, and the eventual presence of electrolytes in the medium [75]. These hydrogels play a vital role in electronic applications; CMC/chitosan and cellulose/alginate hybrid hydrogels are used as electroactive sensors or actuators in electronic devices because they swell or shrink differentially on two electrode sides (anode and cathode) as a consequence of mobile ion transport in an electric field, causing bending toward one electrode [75, 76].

3.5 Magnetic Field Responsive

Magnetic field is another stimulus for hydrogels; the application of magnetic field causes a change in pores of the gel and thereby influences the swelling. The high-strength magnetic field can also induce anisotropy in the supramolecular materials, and the relative orientations occur in the structures [77].

Several forms of magnetic targeting gels have been synthesized; those magnetic gels are also called as ferrogels, which consist of polymer networks, into which magnetic nanoparticles are embedded. The gels are sensitive to magnetic fields and undergo volume change after the application of external magnetic field. Different cellulose derivative-based hydrogels were modified and used as magnetic field-responsive hydrogel such as polysaccharide hydrogels with the combination of Fe_3O_4 nanoparticles [78]. The compounds are generally obtained by incorporating colloidal magnetic solution, named "complex fluid" into the polymer network: through this combination solid-like and fluid-like behavior is induced, the influence of external field on the hydrogels the responsiveness is enhanced. CMC hybrid hydrogels containing $CoFe_2O_4$ nanoparticles, chitosan- and CMC-coated Fe_3O_4 nanoparticles, etc. are used as magnetic field-responsive hydrogels. The Fe_3O_4 magnetic nanoparticles were used to generate heat through the application of an alternating magnetic field; the phenomena adapted were based on the use of magnetic particles in hyperthermia treatment. The application of the magnetic field causes a strong volume change in the hydrogel systems through the thermal

response. These hydrogels have found their applicability in biomedical sectors, such as cell separation [79–81], gene and drug delivery, and magnetic intracellular hyperthermia treatment of cancer [82, 83].

3.6 Mechanical Stress Response

Another stimulus of hydrogel is mechanical force; when the gels are subjected to mechanical stress, the level of energy sources and the molecular interactions are affected. In general two different conditions persist when stress is applied to the hydrogels; one is under the mechanical stresses which the hydrogel's mechanical integrity gets improved which directly relates to the diffusion of macromolecules through the hydrogel network [19], and the other is gel relaxation as the cross-links dissociate and reform elsewhere, and water is lost from the gel, leading to plastic deformation [84]. However, the mechanical stability of the hydrogels is the prime importance for a number of applications [85]. The polymeric network, in the gels, absorbs and retains a large quantity of solvent by increasing their volume but still maintaining the shape and poses some mechanical resistance [51]. The resistance depends on their composition and structure. Irregular cross-linking points and broad distributions of chain length will result in higher swelling; thus, the gels lead to have poor mechanical stability [86], whereas the higher and regular cross-linked gels behave vice versa.

4 Properties of Hydrogels

Hydrogels have a variety of properties including swelling/deswelling behavior, permeability, absorption capacity, mechanical properties, biodegradability, biocompatibility, cytotoxicity, etc., which make them promising materials for a wide variety of applications. The features of the polymer chains and the cross-linking structures in these aqueous solutions play an important role in deciding the properties of the hydrogels. The variations in the properties with respect to various factors are discussed as below.

4.1 Swelling and Deswelling Behavior

Hydrogels have hydrophilic networks with a high capacity of water uptake which can absorb, swell, and retain aqueous solutions up to hundreds of times their own weight, i.e., dry sample.

The swelling behavior of the hydrogels is accessed by immersing the sample into distilled water at room temperature. The swelling process was controlled by frequent weighting. Before weighing, the swollen polymer is removed from water, and the surface moisture was wiped with tissue paper, and its ability of swelling was expressed as the swelling ratio (SR), via Eq. (1) [54, 87].

$$SR = (W_t - W_d)/W_d \tag{1}$$

where W_d is the weight of the dried hydrogel sample (g) and W_t is the weight of the swollen hydrogel sample at time t (g).

Many researchers have investigated the swelling/deswelling behavior of chemically and physically cross-linked hydrogels. Cellulose-based hydrogels have shown various swelling degrees; most important factors that trigger a hydrogel response are pH, temperature, and swelling medium [88]. Apart from the external stimuli, the chemical and structural integrities such as size, shape, porosity, and its distribution may affect the water absorption capabilities.

Water-absorbing ability of cross-linked hydrogel depends on the amount of carboxylic groups of polymer because they remain free after the cross-linking, as they are responsible for swelling [89]. Xiao et al. study reported that the higher cross-linking density had reduced the degree of swelling, due to the inhibition of network expansion [90]. The same effect was also observed by author Suo et al. [26], their study has shown reduced water absorbency with considerable increase in the cross-linking concentration, and similarly irreversible changes occurred during drying. Generally, the swollen hydrogel releases water through a diffusion-driven mechanism, if a gradient of humidity between the inside and the outside of the material exists [91].

The swelling characteristics are determined from hydrogel densities; the densities of the hydrogels are evaluated through simple pycnometric experiments by using nonpolar solvent (n-hexane) for dry hydrogels and water for swollen hydrogels.

The dry hydrogel density (ρ_P) and the swollen hydrogel density (ρ_S) were calculated using the following Eq. (2) [92, 93]:

$$\rho_p(\rho_s) = \frac{m_s}{m_1 - m_2 + m_s} \cdot \rho_L \tag{2}$$

where ρ_L is the liquid solvent density; m_s is the weight of dried hydrogel (for dry hydrogel density), respectively, or the weight of swollen hydrogel (for swollen hydrogel density); m_1 is the weight of the pycnometer filled with solvent; and m_2 is the weight of the pycnometer with sample and solvent.

Hydrogels are also characterized by determining polymer volume fraction in the swollen state and the Flory-Huggins polymer-water interaction parameter (χ) is used to evaluate swelling rate. The polymer volume fraction in the swollen state ($\nu_{2,\ s}$) shows the amount of liquid that can be imbibed in hydrogels, and it is calculated using Eqs. (3 and 4).

$$\nu_{2,S} = Q^{-1} = \frac{\frac{1}{\rho_p}}{\frac{Q_m}{\rho_L} + \frac{1}{\rho_P}} \tag{3}$$

$$\chi = \frac{1}{2} + \frac{\nu_{2,s}}{3} \tag{4}$$

where Q is the volumetric swollen ratio and Q_m is the mass swollen ratio.

The swelling behavior varies based on the temperature; at low temperatures, polymer chains in solution are hydrated and simply entangled with one another. As temperature increases, macromolecules gradually lose their water of hydration, until polymer-polymer hydrophobic associations take place, thus forming the hydrogel network.

The hydrophilic characteristics of cellulose and its derivative-based hydrogels make them appropriate in wide applications such as disposable diapers, hygienic napkins, soil for agriculture and horticulture, gel actuators, water-blocking tapes, drug delivery systems, absorbent pads, etc.

4.2 Water Retention Capacity

Water holding capacity of hydrogel is a significant property to use as absorbent. Particularly when it is used in agricultural application, i.e., during irrigation or rain, the hydrogel absorbs and retains the water; when the soil dries, the hydrogel releases the stored water in a sustained manner through a diffusion mechanism and thereby helps to keep the soil or substrate humid over quite long periods of time [94]. Water held in the expanded hydrogel is intended as a soil reservoir for maximizing the efficiency of plant water uptake. However, due to their extremely high water retention capacity, overdosage of cellulose-based derivatives may have dangerous effects to cultivations. A few research studies have been carried out to determine appropriate hydrogel amounts and application rates for different environmental conditions [54].

In general, the water retention capacity of the hydrogels is characterized using simple experiments; hydrogel samples would be well mixed with 200 g of dry sandy soil and placed in separate containers. Then a quantified amount of tap water will be added to those containers and weighed as (W_1). The containers will be maintained at 25 °C (relative air humidity = 28%) and are weighed at a certain interval (W_i). The water retention ratio [*W(%)*] of sandy soil is calculated using Eq. (5).

$$W(\%) = \frac{W_1 - W_i}{100} \tag{5}$$

The retention capacities of cellulose are generally affected by various factors such as crystallinity, amorphous regions, total surface area, and pore volume. In addition, the cross-linking density also plays a major role in water retention capacity; when there is no enough cross-linking density, loose network formation occurs; thereby gels do not tend to have enough strength to hold water inside the molecular structure [95]; and the effect was also conformed with the study of Nada et al., and their report revealed that the increase in soil water retention are attributed to the hydrophilic polymer network [96]. Besides, the holding capacity of water decreases with increasing temperature. At higher temperature, water holding capacity decreases due to rupture of hydrogen bonds [97, 98]. Moreover, cellulose water retention capacity can be affected by the differences in microstructure of cellulose fibers obtained from different methods of extraction [99]. By introducing microporous structures into the hydrogel, by means of a phase inversion desiccation technique,

the improvement in the water retention capacity is achieved due to capillarity effects. The higher purity and water retention capacity make them suitable for wound healing application; the bacterial cellulose and the series of bacterial cellulose hydrogels wound dressings are currently marketed [54].

4.3 Biodegradation Properties

Biodegradation is the ability of the material to degrade by microorganisms, i.e., material has to be digested or metabolized when implanted in vivo. The labile bonds that are present either in the polymer backbone or in the cross-links tend to break under physiological conditions either enzymatically or chemically [9, 100], in most of the cases wherein hydrolysis occurs.

In general two different methods are carried out to evaluate the rate of biodegradation of hydrogels, namely, enzymatic degradation and microbial degradation:

Method 1: The enzymatic degradation is usually carried out using cellulase C-0901 enzyme, obtained from *Penicillium funiculosum* which is dissolved in an acetic acid – NaOH buffer of pH 5.0 at 37 °C with shaking. About 10 mg of extracted soluble part of the gel is then incubated in enzyme solution at different times. Concentration of the enzyme in buffer is maintained as 0.1 mg ml/1. Then the sample is washed continuously with distilled water and dried in vacuum at 35 °C to a constant weight followed by the incubation.

The result of degradation is expressed as a percentage of the weight loss, and it is evaluated using Eq. (6).

$$\text{Weight loss}\% = (W_0 - W_i)/W_0 \times 100 \tag{6}$$

where W_0 and W_i are the weights of gel before and after enzymatic treatment, respectively.

Method 2: The microbial degradation process utilizes a specially designed microbial oxidative degradation (MOD) analyzer, which consists of four independent columns in which 10 g of the sample along with rinsed sea sand – 450 g – and compost, 130 g, after mixing, are placed. The system is kept under a controlled temperature of 35 °C, and as a result, CO_2 dissipates out of column as the polymer decays. The dissipated CO_2 is collected through a series of columns filled in turn with silica gel, calcium chloride, soda lime, and calcium chloride, respectively. Ammonia formed from the sample was trapped in sulfuric acid solution, and water vapor was absorbed into first two columns (silica gel and calcium chloride). Then the CO_2 was collected quantitatively by soda lime, and water produced during the reaction was caught in the last calcium chloride column. Thus, the mass of produced carbon dioxide was calculated as a difference in the weight of two last columns (containing soda lime and calcium chloride) at the beginning and the end of the test.

The pure compost mixed with sea sand was used as a blank and cellulose as a reference sample [51].

The biodegradation of cellulose-based hydrogels has been widely investigated by many of the researchers [7, 54, 101]. In general, the rate of biodegradation of cellulose depends on degrees of crystallinity. The cellulose-based gels are composed of (1 → 4) glucopyranose repeating units and form fibrous structures with high crystallinity, which is a starting material for biodegradation [102]. The chemical structure (responsible for functional group stability, reactivity, hydrophylicity and swelling behavior, cross-linking network) affects the rate of biodegradation [103].

Most of the cellulose-based hydrogels used in the biomedical application are cross-linked using hyaluronic acid (HA); the presence of HA in the cellulose network provides enzyme-sensitive degradation sites. Various hydrogels from natural polymers have been fabricated by using hyaluronate [104], alginate [105], starch [106, 107], gelatin [108], cellulose [109], chitosan, and their derivatives [110–112]. These sensitive sites are produced due the hyaluronate which could be controlled to a certain extent during synthesis. The degradation rate is dependent on the amount of degradable sites as well as the degree of cross-linking of the network, which affects enzyme diffusivity through the mesh size. The cellulose-based hydrogels leave no residual monomers after cross-linking, which help to rapidly biodegrade in environment [113]. This biodegradation of gels undergoes a significant change in their mechanics, their physical properties, and their chemical structure under specific environmental conditions, and the degradation does not produce any adverse or reproductive effects when utilized in biomedical applications.

The biodegradable materials are those that undergo a significant enough change in their mechanics, their physical properties, and their chemical structure under specific environmental conditions. For many of the biomedical applications such as controlled drug release devices, wound healing dressings, and bioactive scaffolds, the biodegradation of the hydrogel is highly preferred.

4.4 Mechanical Properties

Several researches studied the mechanical properties of the hydrogel including Young's modulus, yield strength, and ultimate tensile strength. Generally the hydrogels are soft and rubbery in nature [114]; their mechanical stiffness depends on the degree of cross-linking [57]. If a gel consists of higher cross-linking density, then the distance between the cross-linked segments remains to be shorter. When a load is applied, these shorter segments require a greater force to deflect. Thus, the higher cross-linked gel structure will have better strength, hardness, or stiffness. For example, when a gel is formed using HA as a cross-linking agent, a low cross-linking density network will be formed which results in softer gels. In order to improve the mechanical properties of such gel, different strategies such as cross-linking or conjugation are used to stabilize HA and obtain a more stable material [115]. The mechanical strength of the gels was improved by increasing the cross-

linking degree [116]. Double network hydrogels with bacterial cellulose and gelatin resulted in higher mechanical strength including low frictional coefficient [7].

In case of physical hydrogels, the dissolution method used for the preparation of hydrogels affects the mechanical properties; in other words the mechanical stability depends on the formation of hydrogen bonds. The mechanical strength of the hydrogels is improved by employing pre-gelation process before performing coagulation [5]. For example, hydrogels prepared from chitin/NaOH/urea solution through coagulation in acidic or aqueous salt solutions had smoother surfaces, more homogeneous structure, and relatively smaller pore sizes, which resulted in improved tensile strength and transparency [117]. The inhomogeneities in the hydrogels will have weak portions of macroscopic network integrity, thus lowering the mechanical properties of the hydrogels.

4.5 Rheological Properties

The rheological property includes shear stress, viscosity, and viscoelastic response; these properties of the gels depend on the types of structure (i.e., association, entanglement, cross-links) present in the system. The rheological response is based on the contributions of cross-links such as covalent bonds and physical cross-links such as electrostatic interactions and hydrogen bonds and some chemical interaction (entanglements) between the molecules.

In order to study the viscoelastic response of the hydrogels, shear modulus measurements are performed at room temperature as a function of frequency. The cross-links between the different polymer chains are also responsible for viscoelastic or pure elastic behavior [13]. For example, the polysaccharide hydrogels behave elastically at small strains and become viscoelastic at large strains, which tend to achieve excellent toughness of the gels [118]. The viscoelastic characteristic of several different hydrogels including agarose and alginate was studied by Ahearne et al., and their study represented that the behavior depends on concentration of cellulose, but these concentration dependencies are smaller than those for viscosity [119]. However, the dynamic viscoelasticity changes with respect to the temperature; the temperature dependencies are different from those of the thermo-reversible gels. Further, the change in deformation over time is also used to characterize the viscoelastic creep response of the hydrogels. For polymers to flow, the chains must move past each other, and cross-linking prevents this movement. The result of restriction in flow will result in the improvement of creep behavior [120].

The cross-links in the hydrogels tend to reduce the intrinsic mobility of the polymer chains and are not able to release stress; consequently the material will have predominant elastic behavior ($G' > G''$) and behaves as a three-dimensional network [115].

Generally, the polymer solutions are essentially viscous at low frequencies, which fits to the scaling laws: $G' \sim \omega^2$ and $G'' \sim \omega$. At high frequencies, elasticity dominates ($G' > G''$); the effect corresponds to Maxwell-type behavior, where G' and G'' are the elastic and viscous moduli, respectively, ω is scaling of the viscous modulus, and ω^2 is scaling dependence of the elastic modulus.

Furthermore, higher concentration of cellulose tends to have higher viscosity, hardness, and cohesiveness. The complex changes occur in both the structure and chemistry of cross-linked hydrogels during rheological characterization, Szcześniak developed methyl cellulose-based hydrogels, and their study found that the addition of chitosan gels based on methylcellulose affected the rheological property. The rheological studies showed that the process was nonlinear, and gels have shown thixotropic properties, i.e., increasing the concentration of chitosan has influenced the viscosity and hardness of the gels [121].

4.6 Biocompatibility and Cytotoxicity

Biocompatibility and cytotoxicity are the important characteristics for biomedical application. Biocompatibility consists basically of two elements, namely, biosafety and bio-functionality. In vitro test for biocompatibility are generally performed in two different ways; in the first method, the hydrogels are positioned in direct contact with the host environmental cells and incubated for a specific period of time at 37 °C; and in the other method, the material is positioned in a suitable physiological solution and then incubated for a specified period of time at 37 °C to permit any leaching from the material. The obtained leachates are used to accomplish the biocompatibility tests in the presence of the cells [14]. The cell viability and cell proliferation from the cytotoxicity test are usually performed. The cell proliferation is visualized by microscopy as well as by carrying out MTT (tetrazolium salt, 3-[4, 5-dimethylthiazol-2-yl]-2, 5-diphenyl tetrazolium bromide) assay, i.e., a colorimetric method which permits quantification of cell growth and proliferation [122].

Hydrogels possess a good biocompatibility since they have hydrophilic surface and low interfacial free energy when in contact with body fluids; thereby, it induces low tendency for proteins and cells to adhere to the surfaces of hydrogels [13]. The excellent biocompatibility and non-toxicity of cellulose and its derivatives have prompted the large use of cellulose-based devices in biomedical areas such as scaffold for cell culture, cartilage model, and implanted in bone defects [123]. A variety of polysaccharides like heparin, chitosan, dextran, and alginate have been explored as hydrogels for tissue engineering owing to their good biocompatibility. The water-soluble cellulose derivatives are mostly biocompatible which can be used as thickener, binding agents, emulsifiers, film formers, suspension aids, surfactants, lubricants, and stabilizers, especially as additives in food, pharmaceutical, and cosmetic industries [7].

5 Conclusion

In this chapter various methods involved in the preparation of cellulose and cellulose derivative-based hydrogels are discussed. In general the gels are synthesized either by physical or chemical cross-linking. The physically cross-linked gels are produced through different mechanisms, i.e., hydrophobic interaction, ionic interaction, or

hydrogen bonding. The chemically cross-linked gels utilize chemicals or radiation to produce 3D network. The chapter discussed different polymerization techniques followed in the preparation of cellulose and cellulose-derived hydrogels, namely, chain-growth polymerization, irradiation polymerization, and step-growth polymerization. The hydrogels have the remarkable ability to respond to different environmental stimuli. The potential response of the cellulose hydrogels w.r.t. external stimuli such as pH, temperature, light, electric field, magnetic field, and mechanical stress is discussed. The chapter addressed the stimuli-responsive materials based on cellulose that have great potential applications in many fields such as drug delivery, electric sensor, water treatment, etc.

Furthermore, various properties of the cellulose-based hydrogels such as swelling/deswelling, water retention capacity, biodegradation, mechanical, rheological, biocompatibility, and cytotoxicity are considered. The property variation with respect to cross-linking density and other parameters such as stimuli, shape, pore size, reinforcement, etc. is discussed.

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Polymer Reaction Engineering Tools to Tailor Smart and Superabsorbent Hydrogels

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Contents

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Abstract

Experimental and theoretical tools to describe and tailor polymer network formation processes are here addressed. Although a special emphasis is given to the synthesis, characterization, and applications of smart and superabsorbent polymers, other networks with higher cross-linker contents are also prospected. Purely synthetic and cellulose-based hydrogels are both considered in this research. The reactor type (e.g., batch or continuous flow micro-reactor), polymerization process (e.g., bulk, inverse suspension, or precipitation polymerization), and polymerization mechanism (e.g., classic free radical polymerization or reversible deactivation radical polymerization RDRP) are highlighted as possible tools to change the morphology and the molecular architecture of polymer networks and hydrogels. The tailoring of cellulose-synthetic hybrid materials is also addressed through the use of RAFT-mediated polymer grafting. Case studies showing the applications of the synthesized materials are presented, namely, molecularly imprinted hydrogel particles for retention of aminopyridines, molecularly imprinted polymers for polyphenols, caffeine or 5-fluorouracil selective uptake/release, as well as modified cellulose adsorbents for polyphenol retention. Cellulose-based hydrogels are also considered as possible vehicles for polyphenol-controlled release. The mechanisms of liberation of polyphenols from these materials are analyzed, namely, when supercritical CO_2 is used in the hydrogel impregnation process.

Keywords

Polymer networks · Hydrogels · Cellulose · Modeling · RAFT polymerization · Molecular imprinting · Controlled release

1 Introduction

Hydrogels are generically defined as low cross-linked hydrophilic polymer networks. Owing to their unique properties, hydrogels present useful applications in medicine and pharmaceutics, hygiene and sanitary industries, agriculture, environment, separation processes, and others [1, 2]. Indeed, due to the swelling capacity of

these kinds of polymer networks, hydrogels are able to absorb a large amount of water without being themselves dissolved. Moreover, some kinds of hydrogels present responsive swelling or shrinking triggered by changes in parameters such as temperature, pH, electric/magnetic fields, ionic strength, etc. These materials, often called "stimuli-responsive" or "smart" hydrogels, exhibit reversible transitions between shrunk and swollen states that are macroscopically apparent. Neutralization of charged groups present in the polymer network due to pH shift and changes in hydrogen-bonding efficiency or in ionic strength are examples of mechanisms inducing such reversible transitions in hydrogels [1].

Polymer networks with the specific ability to absorb huge amounts of water relatively to their dry weight are often called superabsorbent polymers (SAPs). Superabsorbent behavior of such kinds of materials is driven by the water dissolution into the polymer network when it is enhanced by the presence of dissociated ionic pendant functional groups due to a strong solvation process. The difference between a traditional absorbent material (e.g., a polyurethane sponge) and a SAP becomes evident when their absorbencies (mass of absorbed water per mass of dry material) are compared: 10 g/g for polyurethane sponge and up to 1000 g/g for acrylic SAP [2]. It is possible to find polymer gels showing super absorbency features both based on synthetic and natural polymers. Well-known examples of these latter, which generate useful superabsorbent materials, are polysaccharides (such as cellulose), alginates (anionic), chitosan (cationic), and polypeptides (involving physical gelation). On the other hand, polymer networks based upon poly(acrylic acid), polyacrylamide, poly(ethylene oxide), or poly(vinyl alcohol) are commonly used to produce synthetic SAPs. Partially neutralized poly(acrylic acid) networks are especially relevant in SAP industry and present outstanding superabsorbency properties. Hybrid materials containing natural and synthetic polymers, such as starch/polyacrylonitrile or cellulose/poly(acrylic acid), can also be used as superabsorbent materials [2].

Polymers are known to be an important example of "products-by-process" which means that the structure and final properties of the products are mainly defined during the synthesis process [3]. Thus, the molecular architecture of polymer networks, such as smart hydrogels and SAPs, and their end-use properties (e.g., swelling, water absorbency, degree of stimulation, adsorption capabilities, elastic properties) are strongly dependent on the synthesis conditions used in their production. Initial composition, polymerization mechanism (e.g., conventional free radical polymerization or controlled radical polymerization), temperature, and reaction process (e.g., reactor type, solution/bulk/suspension/emulsion polymerization) are examples of key parameters with a crucial effect on the final properties of hydrogels and SAPs. A good knowledge of the mechanisms intervenient in the formation of these kinds of networks is therefore critical in order to make possible a consistent production of advanced materials with tailored properties. Polymer reaction engineering aims at providing the connection between the fundamental kinetic mechanisms occurring during a synthesis process and the microstructure of the resulting polymer and will be here explored in the framework of the production of hydrogel and SAPs. Besides the purely synthetic approach, polymer reaction engineering will be also considered to aid in the production of materials based on synthetic and natural polymers, especially cellulose.

2 Experimental Techniques

2.1 Materials

The following materials were used in the synthesis, purification, and testing of the different kinds of polymers and polymer networks addressed in this research.

Monomers acrylic acid (AA); methacrylic acid (MAA); N-isopropylacrylamide (NIPA); N,N-dimethylacrylamide (DMA); acrylamide (Am); 2-hydroxyethyl methacrylate (HEMA); 2-(dimethylamino)ethyl methacrylate (DMAEMA); and styrene (S) were purchased from Sigma-Aldrich, whereas 4-vinylpyridine (4VP) was provided by Alfa Aesar.

Cross-linkers methylene bisacrylamide (MBAm), trimethylolpropane triacrylate (TMPTA), and ethylene glycol dimethacrylate (EGDMA) were also purchased from Sigma-Aldrich. Polymerization initiators and catalysts 2,2′-azobis(2-methylpropionamidine) dihydrochloride (V50), azobisisobutyronitrile (AIBN), ammonium persulfate (APS), and tetramethylethylenediamine (TEMED) were supplied by Sigma-Aldrich, and 2,2′-azobis[2-(2-imidazolin-2-yl)propane] dihydrochloride (VA-044) was purchased from Wako Chemicals.

RAFT polymerization agents 2-cyano-2-propyl benzodithioate (CYDB), 4-cyano-4-(phenylcarbonothioylthio)pentanoic acid (CPA) and 2-cyano-2-propyl dodecyl trithiocarbonate (CPDT) were purchased from Strem Chemicals. The Sigma-Aldrich commercially available RAFT agents CPA, cyanomethyl dodecyl trithiocarbonate (CDT), S-(thiobenzoyl)thioglycolic acid (TBTGA), and 2-(dodecylthiocarbonothioylthio)-2-methylpropionic acid (DDMAT) were also used in our synthesis tasks. Thioglycolic acid (TA) (Sigma-Aldrich) was used as a chain transfer agent.

Analytical reagent grade acetonitrile (ACN), dimethylformamide (DMF), acetic acid (AcOH), methanol (MeOH), tetrahydrofuran (THF), and acetone were bought from Fisher Chemical (UK). Paraffin oil was received from Vencilab (Portugal). Cyclohexane, n-heptane, dichloromethane, and chloroform were purchased from Sigma-Aldrich. Surfactant sorbitan monooleate (span 80) was purchased from Panreac (Spain). Millipore water (Milli-Q quality) was used in all the experiments unless otherwise mentioned.

Cellulose fibers (medium, cotton linters), microcrystalline cellulose (powder, 20 μm, cotton linters), and Whatman No. 1 cellulose filter paper have been purchased from Sigma-Aldrich and used for the synthesis of cellulose-based hydrogels, the generation of cellulose-based materials with modified physicochemical properties, and also for the production of RAFT-grafted modified cellulose. Sodium hydroxide and urea (Sigma-Aldrich) were used to dissolve cellulose in aqueous solutions. Epichlorohydrin (ECH, Sigma-Aldrich) was used as a cellulose cross-linker. N,N-′-dicyclohexylcarbodiimide (DCC) and 4-(dimethylamino)pyridine (DMAP), both from Sigma-Aldrich, were used as coupling agent and catalyst, respectively, in the Steglich esterification of cellulose with RAFT agents containing carboxylic acid functional groups. Some of the aforementioned monomers were considered in the studies concerning the RAFT-grafting of cellulose, as below discussed in this work.

Different kinds of molecules were considered in retention and release studies involving the polymer networks synthesized as sorbents, namely, 3-aminopyridine (3-APy) and 4-aminopyridine (4-APy) that were obtained from Alfa Aesar. Caffeine (CAF), theophylline (THP), theobromine (THB), ibuprofen (IBU), and isoniazid (INH) were procured from Acros Organics. 5-fluorouracil (5FU), uracil (UR), thymine (THY), and polydatin (POL) were purchased from Sigma-Aldrich.

2.2 Reaction Apparatus and Instruments

Different kinds of reaction apparatus have been used in the synthesis performed in the framework of this research, namely, (i) an atmospheric stirred reactor with maximum capacity of 2.5 L; (ii) a Parr 5100 pressurized glass reactor, mechanically stirred, with 1 L capacity and maximum operation pressure P = 10 bar; and (iii) a supercritical reaction/extraction unit assembled by Paralab SA. This latter unit comprises a Parr 970 mL steel reaction/extraction vessel with mechanical stirring, a pumping system to supply carbon dioxide, control and purge valves, back pressure regulator (BPR), and a trap collector. An automatic control system allows the specification of the set points for the temperature of the coil used to heat the inlet CO_2, temperature of the reactor/extractor, temperature of the BPR, and the temperature of the trap. The amount of CO_2 supplied to the vessel is controlled through a Coriolis flowmeter (mini CORI-FLOW Bronkhorst). The maximum operation temperature and pressure are T = 350 °C and P = 200 bar. (iv) Glass vessels with magnetic stirring were chosen in order to perform batch polymerizations at smaller scales (e.g., 20 mL total volume). (v) A continuous flow micro-reactor including two Knauer HPLC pumps (model Azura P 4. 1S, titanium head) with maximum delivery pressure of 40 MPa and flow rate in the range 0.001 to 10 mL/min is also used in our research. Valco tee devices connect the two lines coming from the pumps with generation of the feed to the micro-reactor. Different tubes with variable internal diameters and lengths (e.g., PTFE tubing with ID ranging from 0.2 to 1.5 mm and L = 20 m) can be used as continuous flow micro-reactors. The micro-reactor tubing is immersed in an oil bath at controlled temperature, and a container at the outlet collects the carrier fluid (e.g., liquid paraffin, cyclohexane) and the polymer particles (e.g., hydrogel particles). A flow of dry argon was used in all the synthesis processes to purge the reactants.

A size exclusion chromatography (SEC) apparatus with refractive index (RI) and multi-angle laser light scattering (MALLS) detection, composed of a Polymer Laboratories PL-GPC-50 integrated SEC system with a differential refractometer with a NIR light source of wavelength 950 ± 30 nm, attached to a Wyatt Technology DAWN8$^+$ HELEOS 658 nm MALLS detector, was used in the characterization of the soluble fraction for the different kinds of polymers synthesized. Information concerning the molecular weight distribution, the average molecular weights, and the *z*-average radius of gyration of the soluble polymer population was thus obtained. Monomer conversion was also estimated through the quantification of the correspondent peaks in the SEC analysis. This SEC system was mostly used to

perform the polymer analysis in organic eluents (e.g., THF and DMF). Through a flow-to-batch conversion kit, the MALLS DAWN8$^+$ HELEOS instrument was also used to perform the *in-line* measurement of the scattered light intensity during hydrogel formation, as below described.

Another SEC apparatus was used for the size fractionation of the soluble polymers considering the direct analysis in aqueous eluents with controlled pH. This system is composed of a Viscotek GPCmax VE 2001 integrated solvent and sample delivery module coupled to a tetra-detector array including refractive index, light scattering, viscosity (IV-DP), and ultraviolet (UV) detection.

An Axiom Analytical Attenuated Total Reflection (ATR) immersion probe, model DRR207, was used to carry out the *in-line* monitoring of the polymerization reactions. A three-arm light guide connected the immersion probe to an ABB Bomem Fourier Transform Infrared (FTIR) spectrophotometer model FTLA2000–104. The spectrophotometer was equipped with an ABB Bomem Mercury-Cadmium Telluride (MCT) detector (model D10B) cooled with liquid nitrogen. The optical system is continuously flushed with argon. This FTIR system was also used to perform the *off-line* analysis of polymer samples.

Other apparatus and techniques used for the polymer network cleaning and characterization include Soxhlet extraction, solid-phase extraction (SPE) in a Visiprep (Supelco, Bellefonte, USA) processing station manifold, and batch and continuous mode adsorption/desorption of selected molecules. In the latter case, networks to be tested were packed in empty GPC columns with bed lengths/internal diameters (mm/mm) ranging from 10/4.6 to 300/4.6, and the uptake/release of the analytes was measured in different solvents. *In-line* and *off-line* measurement of UV absorption was used to quantify these processes. Swelling measurements for the different materials was performed through gravimetric analysis. Standard microscopy (in a Nikon Microscope ECLIPSE 50i) and scanning electronic microscopy (SEM) yielded information concerning the morphology of the different hydrogels and other synthesized polymer networks.

3 Synthetic and Cellulose-Based Hydrogels

A possible division in two main classes of chemically cross-linked hydrogels is based on the provenience of the materials considered in their production: synthetic hydrogels that are obtained through the copolymerization of petrochemical-derived monomers and hydrogels including natural polymers such as polysaccharides or polypeptides. Cellulose-based hydrogels will be here specifically considered in the latter case.

3.1 Overview of Synthesis Routes for Hydrogels

A key tool to design synthetic hydrogels is the selection of the monomers leading to the polymer network. For instance, sensitivity to external stimulation of hydrogels

(a critical feature in many applications) can, in principle, be modulated using different kinds of functional monomers. Indeed, AA and MAA are often used to generate anionic hydrogels with high pH sensitivity, whereas DMAEMA, e.g., is often chosen for obtaining cationic hydrogels with inverse pH stimulation in contrast with the former group. NIPA monomer is often chosen for obtaining hydrogels exhibiting temperature stimulation with a critical transition at around T = 32 °C, which is commonly exploited in biomedical applications. Critical transitions triggered by temperature changes at higher ranges (e.g., around 50 °C) are found with other monomers, namely, with DMA. In certain applications, nontoxic and nonionic hydrogels are sought, and, in this case, HEMA-based polymer networks are good candidates owing to their biocompatibility. When mixed effects are to coexist in the same hydrogel, a polymer network including different functionalities can be used. Amphoteric hydrogels based on AA/DMAEMA and pH/temperature-sensitive AA/NIPA are two examples of such kinds of materials.

Another parameter with a huge impact on synthetic hydrogel properties is the cross-linker content. For instance, commercial superabsorbent polymers (SAPs) are mostly produced through the copolymerization of AA with a very small amount of a cross-linker such as MBAm or TMPTA, e.g. Usually this production process is carried out directly in aqueous phase. Hence, the low water solubility of some cross-linkers is an important issue in this context; organic solvents could also be used, but the process would become less eco-friendly and/or with higher operating costs. Both a very high swelling ratio and a low fraction of soluble polymer must be achieved in SAP synthesis, both implying a mole fraction of cross-linker in the global monomer mixture as low as 0.0025 to 0.5%. The degree of neutralization and initial concentration of AA also plays an important role in SAP performance since polymerizations are often directly performed in alkaline aqueous solutions (e.g., 15 to 40% AA in water with 50 to 70% neutralization using NaOH). Industrially, thermal initiation is preferred, with an operation temperature in the range 40 to 70 °C. The final outcome is a sodium acrylate polymer network. Note that a posttreatment of non-neutralized hydrogels with an alkaline solution is also possible, but a lower efficiency is associated with this alternative.

A higher cross-linker content as compared to the one usually chosen for the soft hydrogels (up to 2%), including the SAPs and other kinds of highly swellable hydrogels, leads to stiffer materials presenting advantageous properties when lower swelling in aqueous media is required. Indeed, in some applications (e.g., biomedical, sensing, etc.) a lower and controlled degree of swelling of the networks is sought, and the cross-linker content used in their synthesis can increase to 5–10%. Moreover, in some other materials such as the molecularly imprinted polymers (MIPs) or other kinds of sorbents, a high geometrical stability of the polymer network must be achieved, and a cross-linker content as high as 80% is practically used.

Changes in the morphology and in the porous structure of polymer network materials (including generic hydrogels and SAPs) can also be used to enhance their performance, namely, the intervenient mass transport mechanisms. Introduction of fillers or porogens in the reaction mixture is usually considered with this goal. Additionally, instead of bulk/solution processes, suspension, inverse suspension, emulsion, precipitation, or dispersion polymerization can be used to produce

hydrogel particles with controlled size and shape. Continuous flow micro-reactors have been chosen in the last few years also aiming at the tailoring of the size and shape of these materials. Figure 1a depicts an image of an acrylic hydrogel powder produced in this research through an inverse suspension process. Figure 1b shows the correspondent water-swollen hydrogel. Note that a fast water absorption process is generally observed with this kind of hydrogels and a huge value for the equilibrium swelling ratio is possible (e.g., SR close to 1000, as described in [4] and references therein).

Owing to the huge abundance of cellulose and its biocompatibility, the development of materials incorporating this natural polymer has been carried out in many recent studies. As far as hydrogels are concerned, several different techniques have been studied in the last few years in order to incorporate cellulose in such materials, as reported in some review papers (see [5, 6] and references therein). Chemically cross-linked cellulose-based hydrogels can be obtained through different synthesis routes, making use of the reaction with the OH groups, namely, through bifunctional molecules such as divinylsulfone, epichlorohydrin, or citric acid. Radical cross-linking processes [5] avoid the toxicity problems associated with some bifunctional cross-linkers and offer some advantages for producing cellulose-based hydrogels.

A major problem to be faced when hydrogels are prepared directly from native cellulose is the very low solubility of this polymer in common solvents due to its extensive hydrogen-bonding interactions. Fortunately, new solvents of cellulose have been lately found such as LiCl/dimethylacetamide (LiCl/DMAc), N-methylmorpholine-N-oxide (NMMO), ionic liquids (ILs), and alkali/urea aqueous mixtures [5]. Hydrogel generation can therefore be easily carried out after cellulose dissolution.

3.2 Case Studies with Acrylic and Cellulose/Epichlorohydrin Hydrogels

In Table 1 are presented some recipes used in our research to generate cellulose-based hydrogels. The alkali/urea method for dissolution of cellulose in aqueous systems was chosen including, as reported in the literature [7–9], cycles of cooling

Fig. 1 (**a**) Dried acrylic hydrogel powder obtained through inverse suspension. (**b**) Water-swollen acrylic hydrogel. (**c**) Water-swollen cellulose/epichlorohydrin hydrogel

(e.g., at T = −30 °C) followed by room temperature thawing. Afterward, epichlorohydrin was used as cross-linker, following also the methods before developed [7–9] (24 h reaction time was used in our synthesis). The image of a typical cellulose-based hydrogel obtained under these conditions is presented in Fig. 1c. These results illustrate the possibility for effective cellulose-based hydrogel preparation, using relatively simple processes, following recent research results on this subject [7–9].

The dynamics of swelling and deswelling is a key aspect in the application of hydrogels as superabsorbents, sensors, controlled release vehicles, chromatographic supports, general adsorbents, or biomedical technologies [5]. Obviously, this dynamics and the equilibrium swelling ratio depend on many factors, such as the chemical composition of the hydrogel, the cross-linking density of the network, the morphology and porosity of the materials, etc. Additionally, the swelling conditions, namely, the composition of the solvent, the pH, temperature, and ionic strength, also play a central role on the hydrogel swelling.

Figure 2 illustrates the dynamics of swelling with different kinds of hydrogels synthesized in our research. In Fig. 2a is presented the behavior of an AA-based acrylic hydrogel, obtained in the powdered form through inverse suspension, when dipped either in deionized water or in a 0.9% NaCl aqueous solution. A very fast swelling process is observed, and very high equilibrium swelling ratios are obtained in both conditions, namely, SR~200 in deionized water and SR~100 in 0.9% NaCl aqueous solution. Note however the large drop of swelling ratio when the ionic strength of the solution is increased. Figure 2b shows the dynamics of swelling for two different cellulose-based hydrogels, generated from the cross-linking of microcrystalline and filter paper cellulose with ECH (samples HCEL-5 and HCEL-8 in Table 1). In both cases, the swelling process starts from the dried hydrogels in the form of a single cylinder piece with typical diameter × thickness = 10 × 3 mm × mm. These results put into evidence that the swelling of cellulose-based hydrogels depends strongly on the synthesis conditions used, namely, the kind of cellulose, the dissolution conditions and, among others, the cross-linking conditions. Obviously, changes of the synthesis conditions can be considered to modulate the

Table 1 Synthesis conditions used for cellulose dissolution in aqueous solutions followed by hydrogel preparation with ECH as cross-linker

Hydrogel alias	Cellulose type	NaOH (wt.%)	Urea (wt. %)	CEL (wt. %)	Solution vol. (mL)	ECH vol. (mL)	Preparation T (°C)
HCEL-1	Microcrystalline	7	12	2	10	1	60
HCEL-2	Fibers	7	12	2	10	1	60
HCEL-3	Filter paper	7	12	2	10	1	60
HCEL-4	Fibers	6	4	2	10	1	60
HCEL-5	Microcrystalline	7	12	4	10	1	60
HCEL-6	Fibers	8.6	–	3	6.7	2.14	80
HCEL-7	Microcrystalline	8.6	–	3	6.7	2.14	80
HCEL-8	Filter paper	8.6	–	3	6.7	2.14	80

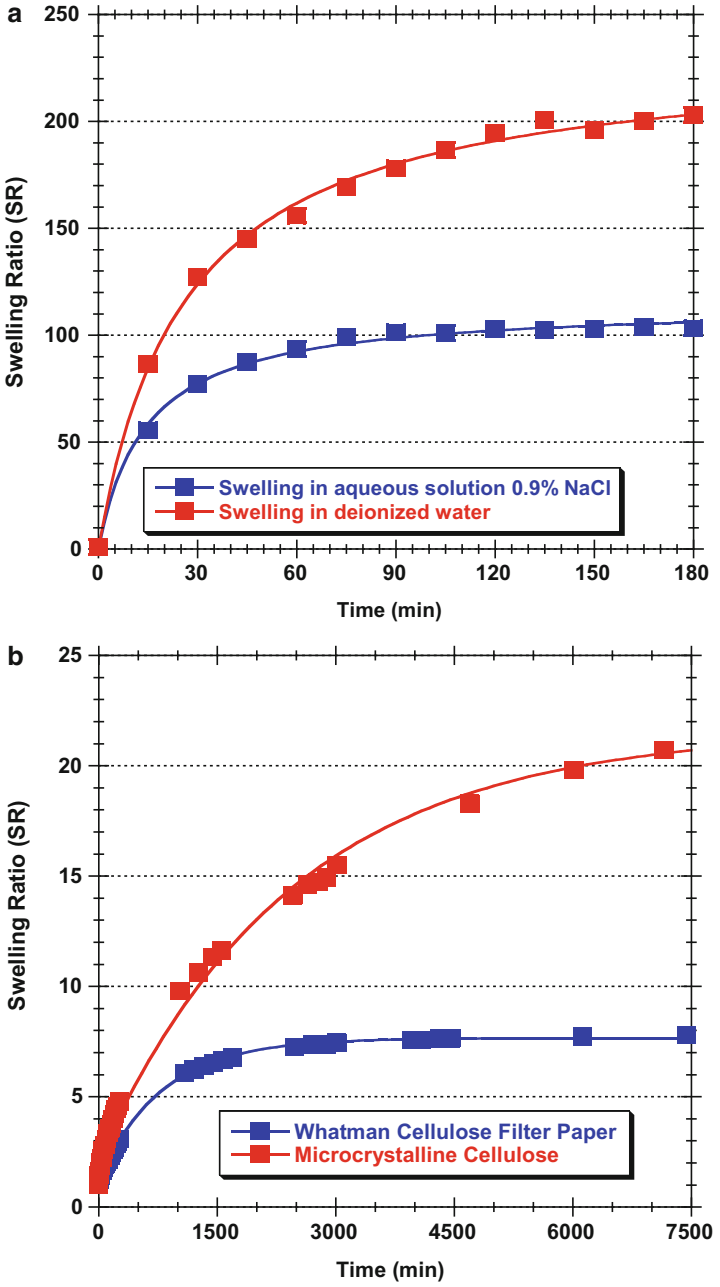

Fig. 2 (**a**) Dynamics of the swelling ratio of an acrylic hydrogel in deionized water and in a 0.9% NaCl aqueous solution. (**b**) Dynamics of the swelling ratio for two different cellulose/epichlorohydrin hydrogels

swelling of the cellulose-based hydrogels in view of the desired application (superabsorbency, controlled release, biomedical, etc.).

The comparison of results presented in Fig. 2a for acrylic hydrogels and in Fig. 2b for cellulose-based hydrogels highlights that considerable differences are observed in the swelling of the two classes of materials. With the selected samples, a much faster swelling dynamics is observed for the acrylic hydrogel comparatively to the cellulose-based networks. Additionally, the equilibrium swelling ratio of the acrylic hydrogels is roughly 10 times higher than that of cellulose materials. Note however that besides the intrinsic chemical differences between the two classes of networks, the morphologies of the products tested are also very distinct (acrylic powder vs. a single piece of cellulose hydrogel). These morphological differences also have a large impact on the dynamics of swelling thus affecting the performance of both kinds of hydrogels. Indeed, several different kinds of parameters are being considered in the scientific community to design these materials. The generation of hybrid hydrogels incorporating both synthetic polymers and cellulose is a promising route in view of the modulation of the properties and the use of sustainable natural resources. The use of synthetic/cellulose interpenetrating polymer networks (IPNs) and grafting of synthetic polymers in cellulose (as below discussed in the present work) are two important approaches to target this issue [5, 6].

The above-presented results illustrate some basic principles involved in the synthesis and application of both synthetic and cellulose-based hydrogels. However, there is plenty of room to improve the structure and properties of these polymer networks concerning the synthetic and the cellulose-based products as well as the hybrid materials. Indeed, a major opportunity to control and design the molecular architecture of polymers was created with the discovery of the reversible deactivation radical polymerization (RDRP) mechanisms. These techniques allow the precise synthesis of many complex structures such as block copolymers, stars, and comb polymers. RDRP mechanisms (e.g., RAFT, ATRP, NMRP) can also be used to achieve improvements of polymer networks, namely, by increasing their structural homogeneity due to the control of the cross-linking process and of the size distribution of the chains between cross-linking points. New grafting processes, functionalization of polymer networks, and creation of complex architectures (e.g., surface brushing) are also possible in the framework of RDRP techniques, especially RAFT polymerization. These new opportunities will be discussed along this work in the context of both the synthetic and the cellulose-based polymer networks.

4 Dynamics of Network Formation and Structural Inhomogeneities

4.1 Light Scattering Measurements and Network Inhomogeneity

The timeline for synthetic network and gel production begins with the vulcanization of natural rubber in the nineteenth century. The synthesis of Bakelite in the beginning of the twentieth century, ion-exchange resins in the 1930s, contact lenses in the

1950s, SAPs and volume phase transition gels in the 1970s, responsive polymers in the 1980s, high strength gels in the beginning of the twenty-first century, and nowadays' synthesis of nearly ideal polymer networks are some important milestones in this context [10]. Different kinds of theories were also developed along the time with the goal of describing the formation, structure, and performance of these materials. Since the 1930s, molecular and phenomenological theories (elasticity, swelling, etc.) were developed by Kuhn, Flory, James, Guth, Treloar, and many others [10]. The entanglement concept in polymer networks was worked out in the 1970s (e.g., Graessley theory), and in a third step, starting in the 1990s until nowadays, the inhomogeneities of polymer networks were addressed using, e.g., Cohen-Colby and Panyukov-Rabin theories [10]. Most of these theories were developed considering the concept of "ideal polymer network" where the sub-chains between cross-links have the same length and defects and entanglements are absent. However, it is known that real polymer networks contain different kinds of irregularities (e.g., distinct kinds of cross-links, through their chemical nature, connectivity, and mobility) due to poor control of the cross-linking process during synthesis, occurrence of side reactions, and inevitable topological complexity of the network structure (such as the presence of short loops). Therefore, the behavior of real polymer networks is far from the expected for a treelike architecture, and an important deleterious effect of the structural inhomogeneities on material performance is often observed.

Thus, the assessment and control of structural inhomogeneities in polymer networks and gels is an important issue that can be addressed considering different approaches. Light scattering studies provide valuable information in this context because an increase in the scattered intensity is commonly observed as a consequence of a cross-linking process. It is accepted that the observed excess scattering is an effect of the polymer structure and shows the degree of heterogeneity of the networks [11]. Often, the practical application of such methods is based upon the evaluation of the difference between the excess scattering of the gel and of the analogous linear polymer solution (formed in the absence of cross-linker), as described in the following equation:

$$R_{ex,q} = R_{gel,q} - R_{sol,q} \tag{1}$$

The Rayleigh ratios for the gel and for the analogous linear polymer solution at the scattering angle θ are obtained through Eq. (2):

$$R_{ex,\theta} = \frac{\left(I_\theta - I_{\theta,solvent}\right) r^2}{I_0 V} \tag{2}$$

Variable I_θ above represents the scattered light intensity at the scattering angle θ, I_0 the intensity of the incident beam, V the volume of the scattering medium, and r the distance between the scattering volume and the detector. Usually, calculations are performed using as independent variable the scattering factor q instead of the scattering angle:

$$q = \frac{4\pi n}{\lambda_0} \sin(\theta/2) \tag{3}$$

With n, λ_0, and θ representing the solvent index of refraction, the wavelength of the incident light, and the scattering angle, respectively.

In practice, it is possible to carry out the *in-line* measurement of the scattered light intensity (I_θ) during the polymer formation [12, 13]. A typical analysis of such kind is presented in Fig. 3 for the polymerization of partially neutralized AA with initiation by APS/TEMED at room temperature. These measurements were performed in a DAWN8+ light scattering instrument and using a flow-to-batch conversion accessory.

From Fig. 3, it can be observed that, after an induction period, the polymerization is accompanied by an increase of the scattered light intensity, eventually reaching a maximum. This maximum corresponds to the critical overlap polymer concentration, and gelation occurs at or slightly beyond this point [12, 13]. Due to the growth of polymer concentration, the scattered light intensity starts to decrease after the critical point. Such kinds of measurements are helpful in the assessment of the spatial heterogeneity of the formed synthetic polymer but can also be used to investigate the formation of gels based on natural polymers, such as cellulose/epichlorohydrin hydrogels (for instance). Additional information concerning the mesh size of the networks and the average molecular weight between cross-linking points ($\bar{M}_c$) can be obtained using dynamic light scattering and mechanical measurements, respectively [12, 13].

4.2 Swelling Analysis

Swelling analysis can also be used to obtain information concerning the average molecular weight between cross-linking points, according the Flory-Rehner theory (see [14, 15] and also Chap. 11 in Ref. [1]):

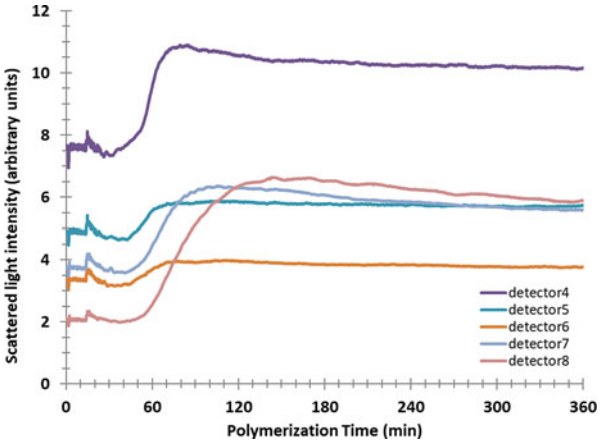

Fig. 3 In-line measurement of the scattered light intensity (I_θ) recorded at different angles (detectors) as a function of the reaction time for the polymerization of partially neutralized AA with initiation by APS/TEMED at room temperature

$$\frac{1}{\bar{M}_c} = \frac{2}{\bar{M}_n} - \frac{\bar{v}\left[\ln(1 - v_N) + v_N + \chi v_N^2\right]}{V_S\left(v_N^{1/3} - v_N/2\right)} \tag{4}$$

In the above equation, V_S stands for the molar volume of the solvent, $\bar{v}$ for the specific volume of the polymer network, v_N for the volume fraction of polymer network in the swollen mass, $\bar{M}_n$ for the molecular weight of the primary polymer chains, and χ for the solvent-polymer interaction parameter (according to Flory-Huggins theory). The volume fraction of polymer network in the swollen mass (v_N) can be experimentally estimated through swelling experiments and is related to the mass swelling ratio by the equation:

$$v_N = \frac{1}{1 + (SR - 1)\dfrac{\rho_N}{\rho_S}} \tag{5}$$

In the above equation ρ_N and ρ_S represent the mass densities of the polymer network and of the solvent, respectively. If the solvent-polymer interaction parameter (χ) is known (estimation methods are also often used [16]), Eq. (4) provides a simple form to measure the $\bar{M}_c$ network parameter. This analysis has been considered in very recent works [17] to assess the homogeneity of polymer networks, namely, through the comparison of gels produced by free radical processes and reversible deactivation radical polymerization (e.g., RAFT polymerization).

4.3 FTIR Analysis of Network Formation

In general, FTIR analysis provides important information concerning polymer formation and final composition of the materials. This technique can also be applied to elucidate the mechanisms of formation of networks and their final chemical functionalities [18–24]. Besides the usual *off-line* analysis of the products [23, 24], *in-line* FTIR monitoring of network development can also be performed [18–22].

In Fig. 4 are presented results concerning the *in-line* FTIR-ATR monitoring of free radical processes involved in typical synthetic hydrogels production, namely, the aqueous polymerization of AA/MBAm (Fig. 4a) and the terpolymerization of MAA/AAm/MBAm (Fig. 4b). These results illustrate the dynamics of change observed in specific peak assignments, showing the polymerization progress.

4.4 Size Exclusion Chromatography

Size exclusion chromatography (SEC) is a powerful technique disclosing important information concerning the soluble polymer species in a specific eluent. In general, for linear polymers, information concerning the entire polymer population is obtained if a proper solvent is available. With nonlinear polymers, although the

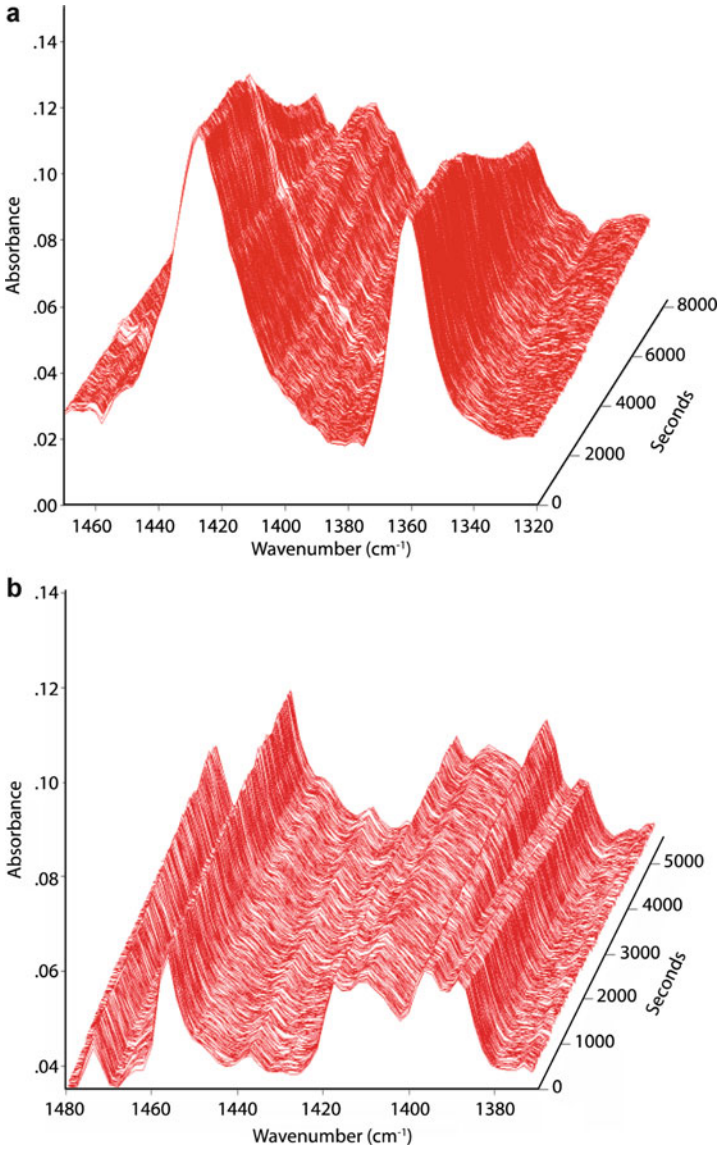

Fig. 4 *In-line* FTIR-ATR monitoring of free radical polymerization processes considered in synthetic hydrogels production: (**a**) aqueous polymerization at room temperature of AA/MBAm (99.5/0.5 mol %), 15% monomer concentration, and 0.1% APS/TEMED. (**b**) Aqueous polymerization at room temperature of MAA/AAm/MBAm initiated by 0.66% APS/TEMED. Initial monomer composition: 13% v/v of MAA in water, 5% w/w of AAm, and 0.5 mol% of MBAm in global monomer composition

soluble phase in the selected solvent can be analyzed by SEC, the superposition of chromatograms of species with different molecular masses or structures but same effective sizes in solution complicates seriously the quantitative analysis. Molecular size distribution and *z*-average radius of gyration are typical structural features that can be investigated through SEC with multiple detection (usually RI and MALLS). Monomer conversion can also be estimated using SEC when the peaks of the involved monomers are detectable in the chromatographic traces.

Some important features provided by SEC analysis in the framework of synthetic hydrogel formation (or their linear counterparts) are presented in Fig. 5. Figure 5a shows the possibility for monomer conversion measurement when the SEC traces of polymer and monomer(s) are identifiable. An inverse suspension RAFT polymerization process, involving the AA and NIPA monomers, is here considered for illustration purposes. Depletion of both monomers in samples collected at different polymerization times is clearly seen. Note that, in the formation of hydrogels, the amount of cross-linker is very small in comparison with the main monomers, and its reliable measurement by SEC is not possible in these conditions.

Figure 5b depicts SEC chromatographic traces for a sample correspondent to the AA/MBAm RAFT polymerization in DMF. The RI and light scattering signals are simultaneously presented in this plot. The existence of soluble polymer is identifiable through the LS and RI signals with the latter also showing the AA monomer peak. Note, however, the huge difference between the RI and LS signals showing the formation of a polymer cluster at a very low concentration (almost nil RI response) but very high molecular size (high LS response). Similar analysis provides useful information concerning the development of the polymer population during the synthesis, namely, an imminent gel formation due to the cross-linking process (predated by the formation of a very large polymer cluster).

In Fig. 5c are compared the LS signals correspondent to samples collected at different polymerization times during inverse suspension DMA RAFT polymerization. The dynamics of the development of a secondary polymer population is here illustrated (see also [21]). Note that these measurements can enlighten key kinetic steps involved in the polymerization mechanisms such as the eventual formation of three-arm adducts during RAFT polymerization due to the termination of intermediate radicals (see [25] and references therein for a detailed discussion on these issues).

Figure 5d compares the SEC analysis correspondent to the FRP of AA in the absence and in the presence of a chain transfer agent (thioglycolic acid was used). The effect of the chain transfer agent on the molecular weight distribution of the polymer is here illustrated, and a possible manipulation of the polymer molecular size through this mechanism is highlighted (a substantial decrease on molecular size is clearly observable). Note that the knowledge on the formation processes and structure of the linear counterparts of the main polymer chains involved in hydrogel formation is critical to understand and tailor the properties of these networks. Indeed, primary chains (those remaining when the cross-links are severed in a network) play a central role in gel formation (as described in Sect. 5) and also in networks properties (elasticity, swelling, and so on). Thus, comparative measurements, such

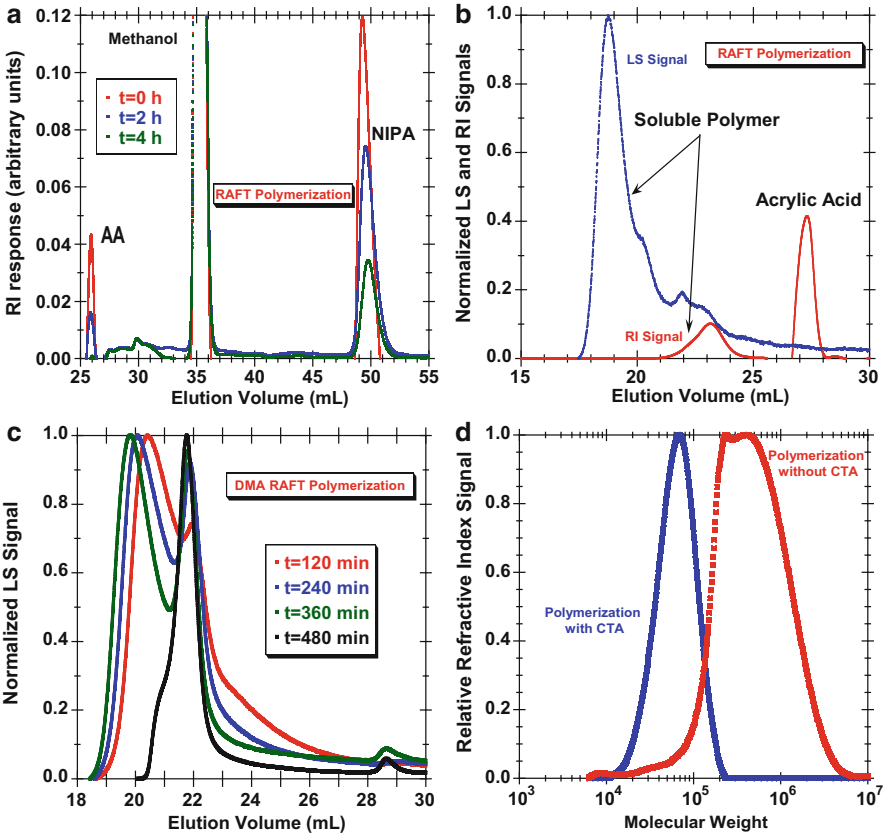

Fig. 5 Results of different SEC analysis carried out for samples of synthetic hydrogels or their linear polymer counterparts. (**a**) Measurement of AA and NIPA concentration in a RAFT copolymerization process involving these two monomers. (**b**) Light scattering and RI signals for an AA-based hydrogel synthesized through RAFT polymerization. (**c**) Light scattering signal for samples correspondent to the DMA RAFT polymerization collected at different polymerization instants. (**d**) Measured effect of the presence of a chain transfer agent (thioglycolic acid) on the molecular weight distribution of an AA polymer

as those provided in Fig. 5a and d for linear polymerization, are helpful to design the hydrogels obtained in similar conditions. In this context, tailoring of the average molecular weight between cross-linking points ($\bar{M}_c$) using RAFT polymerization, as above discussed, is an important opportunity that is being considered in the scientific community.

The knowledge on the kinetics of polymerization plays also an important role on the design and control of hydrogel formation. Some information provided by SEC analysis is illustrated in Fig. 6. The measured dynamics of monomer conversion for AA/MBAm copolymerization with three low contents of MBAm is shown in Fig. 6a. The effect of the degree of neutralization with NaOH in the polymerization

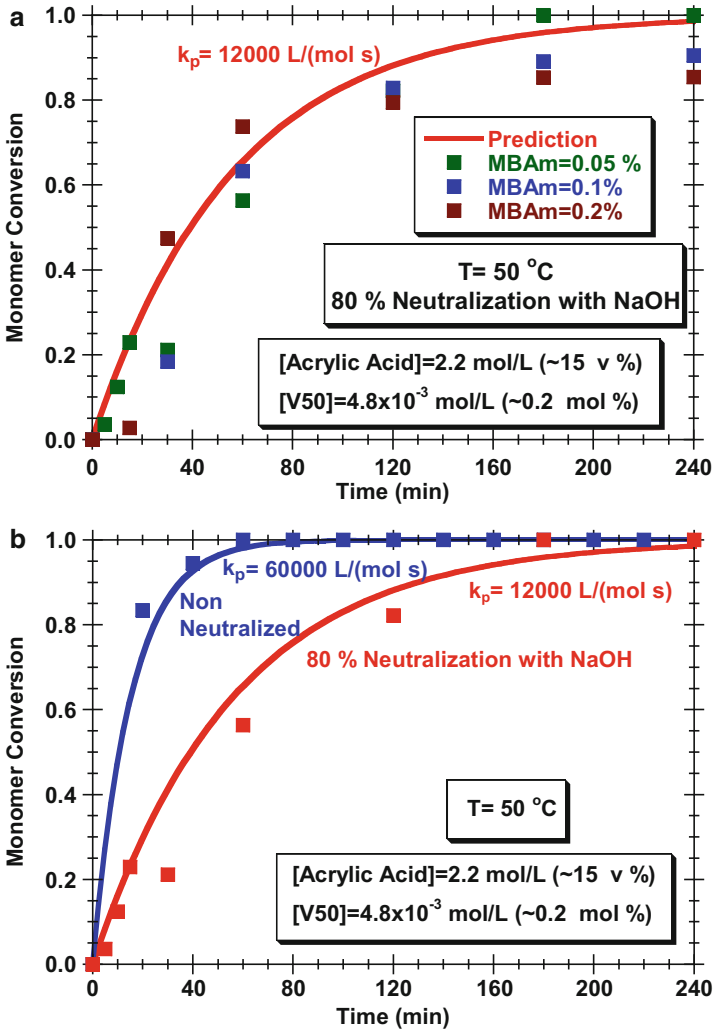

Fig. 6 (**a**) Kinetics of polymerization in an AA/MBAm hydrogel formation obtained by SEC. Cross-linking processes with mole fraction of MBAm ranging from 0.05 to 0.2% were considered. Polymerizations at T = 50 °C with V50 as initiator, concentration of AA ~ 15 v%, and 80% neutralization with NaOH. (**b**) SEC measured effect of the degree of neutralization on the rate of AA polymerization. Non-neutralized and 80% neutralized polymerizations are compared

kinetics is presented in Fig. 6b, evidencing the fall of the polymerization rate when the degree of neutralization is increased. Such kind of experimental data can be used to estimate kinetic parameters (e.g., the propagation rate constants) and to develop models to aid in the design of these polymerization processes, as explored in the next section.

5 Calculation Tools to Describe Network Formation

5.1 Overview

This section presents calculation methods often used to describe the formation of synthetic hydrogels. The modeling of general polymerization process where the branching and cross-linking mechanisms are intervenient is analyzed. The applicability of such tools to design hybrid materials including natural polymers, such as cellulose, is also discussed. Modeling tools for nonlinear RDRP are also briefly addressed.

5.2 Flory-Stockmayer Theory of Gelation

Synthesis of materials presently known to consist of cross-linked synthetic polymers is documented since the first half of the nineteenth century starting with the vulcanization of natural rubber by brothers Charles and Nelson Goodyear.

Along with other important contemporary contributions by W.H. Carothers, W. Kuhn, and G. V. Schulz, it was P.J. Flory [26–30] who laid out the modern foundations of the analysis of polymerization reactions, using either population balances of species [30] or elementary probabilistic deductions [26–29]. The formation of "infinitely" large three-dimensional networks (gels) and the general condition for gelation in condensation polymerization of a symmetrical monomer with f self-reacting groups A_f (such as a silanetriol, with $f = 3$) was established:

$$p_g = \frac{1}{f-1} \tag{6}$$

Here, p is the probability that a chain starting from a branch unit would lead to another branch unit rather than to a terminal group. The derivation of this critical condition is based on a random branching process, as depicted in Fig. 7a for a trifunctional system [26]. Soon afterward, W.H. Stockmayer [31–33] generalized Flory's theory and the whole approach become known as the Flory-Stockmayer (FS) theory of gelation. Using a probabilistic and combinatorial reasoning, W. Stockmayer found in particular an expression for the weight fraction of all isomer species carrying n units for this step-growth polymerization [31]:

$$w(n) = \frac{f(fn-n)!}{(n-1)!(fn-2n+2)!} p^{n-1}(1-p)^{(f-2)n+2} \tag{7}$$

It is worth noting that W. Stockmayer took the trouble to show that Eq. (7) can also be found through the population balance of polymer species, leading him and his contemporaries to believe that both reasonings are always equivalent and lead to the same results, something which would take nearly three decades to be understood as a mistake, as we discuss in the next section. Nevertheless, these results are

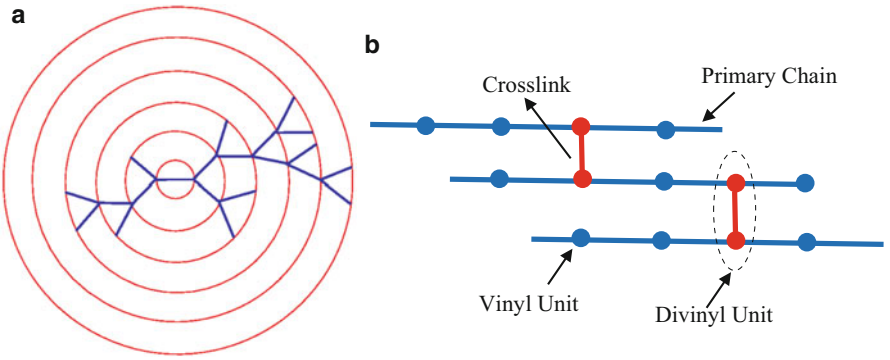

Fig. 7 (**a**) Depiction of the condensation of a trifunctional monomer ($f = 3$) leading to a branched polymer according the Flory's theory: formation of an infinite network is possible if $p > 1/2$ [26]. (**b**) Depiction of the primary chains and cross-links in a network formed through a vinyl/divinyl copolymerization. The same formalism can be used to describe the cross-linking of linear polymer chains (e.g., the cross-linking of cellulose chains)

rigorous for equilibrium step-growth polymerizations and a good approximation even for many chain polymerizations; thence, it is worth pursuing the presentation of these classical findings.

Flory, using the formation of three-dimensional polymers with tetrafunctional branch units as a case study [28], also initiated the extension of the theory of gelation to chain polymerizations. The copolymerization of vinyl and divinyl compounds and the vulcanization of rubber was pointed as two examples involving tetrafunctional branching. Such chemical systems were also later discussed by Stockmayer and co-workers [32, 33], and an expression to predict the critical gelation conversion was derived in the framework of the FS theory:

$$p_g = \frac{1}{y_f\left(\bar{x}_w^* - 1\right)} \tag{8}$$

In Eq. (8), y_f represents the mole fraction of double bonds residing on the divinyl monomer, p_g the conversion of double bonds at the gel point, and $\bar{x}_w^*$ the weight-average chain length of the primary chains. Primary chains are defined as the polymer chains that would remain if every double-reacted divinyl units (cross-links) were severed in the network, as depicted in Fig. 7b (see also the early contribution of Walling for a simplified scheme of vinyl/divinyl copolymerization [34, 35]). Note that the formalism of the FS theory for cross-linking processes can be applied both to the cross-linking of preformed linear polymer chains (e.g., the cross-linking of cellulose that play the role of primary chains) and to the network formation due to vinyl/divinyl copolymerization. In the latter case, the primary chains are considered to be formed during the course of the cross-linking process. Indeed, Flory [28] and Stockmayer [33] derived the expression for the molecular size distribution of the network resulting from the random cross-linking of primary molecules with uniform length:

$$w_P(m) = \frac{m^{m-1}}{\gamma m!}(\gamma e^{-\gamma})^m \tag{9}$$

In Eq. (9), $w_P(m)$ represents the weight fraction of polymer molecules containing m primary chains and γ and the cross-linking index, defined as the number of cross-linked units per primary molecule. On other hand, the cross-linking density of the network (ρ) is defined as the fraction of units that are cross-linked (each cross-linkage bears two cross-linked units, as depicted in Fig. 7b). These two parameters are related through $\gamma = \rho\bar{x}_n^*$, with $\bar{x}_n^*$ representing the number-average chain length of the primary chains.

Note that the critical condition for gelation described by Eq. (8) can be rewritten as $\rho_g\left(\bar{x}_w^* - 1\right) = 1$ with $\rho_g = p_g y_f$ representing the cross-linking density of the network for the vinyl/divinyl system at the gel point (indeed, $p_g y_f$ is the fraction of created cross-linked units at gelation due to the vinyl polymerization process). These equivalences also illustrate the applicability of the FS formalism to the cross-linking of preformed primary chains or the copolymerization of vinyl/divinyl monomers.

For primary polymer chains with uniform length ($\bar{x}_n^* = \bar{x}_w^*$), the critical condition for gelation due to cross-linking is thus $\rho_g\left(\bar{x}_w^* - 1\right) \sim \rho_g\bar{x}_w^* = \rho_g\bar{x}_n^* = 1$, and therefore $\gamma_g = \rho_g\bar{x}_n^* = 1$. For heterogeneous primary chains, the critical cross-linking index is lower than one because $\bar{x}_w^* > \bar{x}_n^*$ (e.g., for primary chains with most probable distribution $\bar{x}_w^* = 2\bar{x}_n^*$, and gelation occurs with cross-linking index $\gamma_g = 1/2$). Note that the theory dealing with the random cross-linking of primary polymer molecules with arbitrary distribution sizes [36] is especially important to describe some processes of gel formation from cellulose chains (e.g., through the cross-linking reactions involving the cellulose hydroxyl groups and epoxides, isocyanates, or carboxylic acids). In particular, it is possible to show that the molecular size distribution for the random cross-linking of a population of primary chains with the most probable distribution is correspondent to the condensation of $A_2 + A_4$ units [36].

FS theory leads to some simple relations valid for the post-gelation period, such as the weight fraction of sol in the random cross-linking of primary chains with uniform length:

$$w_s = e^{-\gamma(1-w_s)} \tag{10}$$

In this equation, w_s represents the weight fraction of sol, while $w_g = 1 - w_s$ stands for the weight fraction of gel. If the size of the primary chains is arbitrarily distributed, the analogue equation for the weight fraction of sol is:

$$w_s = \sum_{n=1}^{\infty} w(n)[1 - \rho(1 - w_s)]^n \tag{11}$$

$w(n)$ in the above equation represents the weight fraction of primary molecules with n units. The applicability of this equation is limited to systems with low cross-linking density ($\rho \ll 1$). Other expressions allow the calculation of the cross-linking density of the sol and the gel as well as the number and weight-average degree of polymerization of the sol before and also after gelation [36]. In Figs. 8, 9, 10, 11, 12, 13,

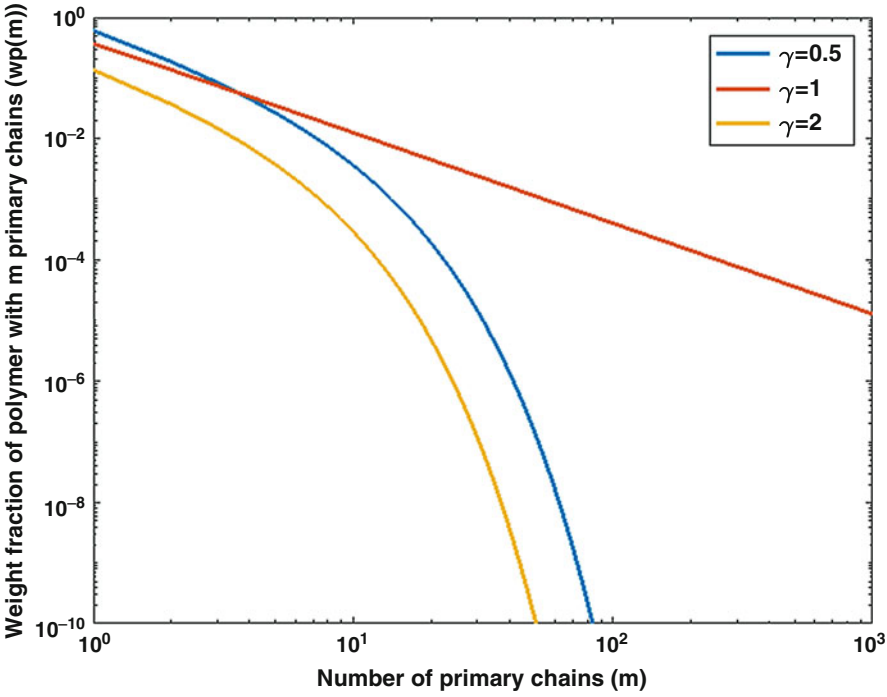

Fig. 8 Weight fraction of polymer with m primary chains, $w_P(m)$, in the random cross-linking of primary molecules with uniform length. Three values for the cross-linking index were selected in order to illustrate the pre-gelation period ($\gamma = 0.5$), gel point ($\gamma = 1$), and the post-gelation ($\gamma = 2$). The overall cross-linking density (ρ) is related with γ through $\gamma = \rho \bar{x}_n^*$ (e.g., with $\bar{x}_n^* = 500$, $\rho = 0.001$, 0.002, and 0.004 for $\gamma = 0.5$, 1, and 2, respectively)

and 14 are illustrated some calculations in the framework of the FS theory, highlighting the possibility to describe relevant variables in cross-linking processes, such as weight fraction of gel, cross-linking density, and molecular weight of the sol and gel.

Note that the above-described calculation methods in the framework of the FS gelation theory can also be applied to the irreversible batch formation of gels such as cellulose-epichlorohydrin polymers. Using a plausible chain length distribution for the primary chains (the cellulose polymer) and taking into account the amount of cross-linker considered in the polymerization (e.g., epichlorohydrin), which defines the number of cross-linkages and therefore the cross-linking density (ρ), the extent of gel formation and the sol/gel properties can be calculated, as above discussed. In practice, the extent of reaction between the OH and epoxy groups and the occurrence of side reactions with epichlorohydrin (e.g., the hydrolysis process in alkaline conditions [7, 8]) are factors with important influence on the real cross-linking density values attained in the gel formation.

The combinatorial reasoning used by Stockmayer is not at all convenient and in 1963 the mathematician I. J. Good and the physical chemist M. Gordon have replaced it with the application of the more powerful *Theory of the Branching*

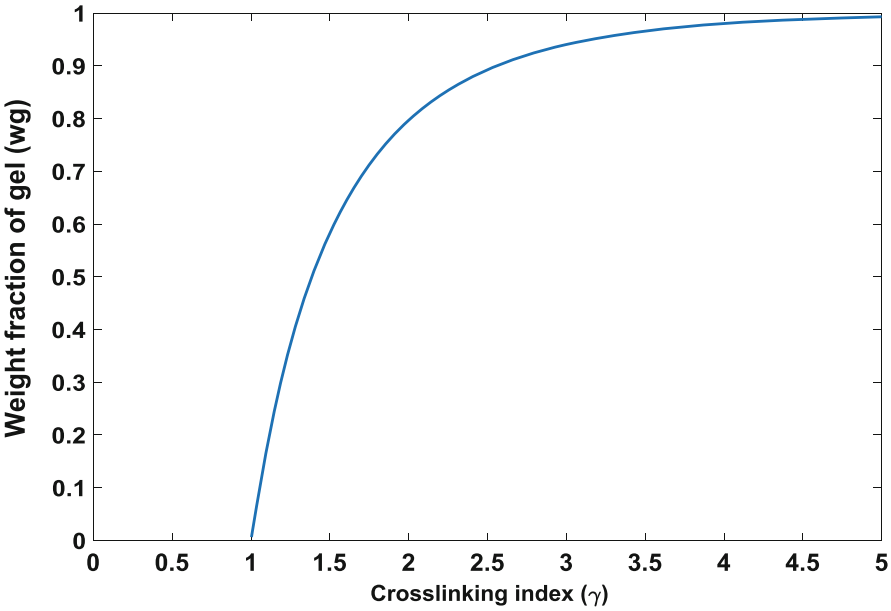

Fig. 9 Weight fraction of gel (w_g) as a function of the cross-linking index (γ) in the random cross-linking of primary molecules with uniform length

Processes (TBP) [37, 38] (with a later impoverished implementation called "recursive approach" by Macosko and Miller [39]). Then, it became possible to tackle chemical systems where different chemical groups and/or substitution effects were present. It then became apparent that some results were not compatible with the analysis by rate equations (see next section).

Another even more important issue is the tackling of intramolecular reactions. Slight disagreements with observed gelation of step-growth polymerizations were long known [27, 28], but the disagreement for chain polymerizations turned out to be very serious [34, 35].

Another issue arises from the stochastic character of real polymerizations leading to fluctuations according to position which diffusion is unable to erase instantaneously. Gelation will not occur for a real network everywhere at the same time even if starting with a perfectly homogeneous mixture. Numerous fundamental studies have used Monte Carlo simulation in a restricted space mesh to gain insight on those phenomena; they have not yet made their way into engineering practice.

5.3 Calculation Methods for Kinetically Controlled Nonrandom Processes

In spite of the appealing simplicity of the FS gelation theory, this approach presents important shortcomings in the description of some cross-linking processes, namely,

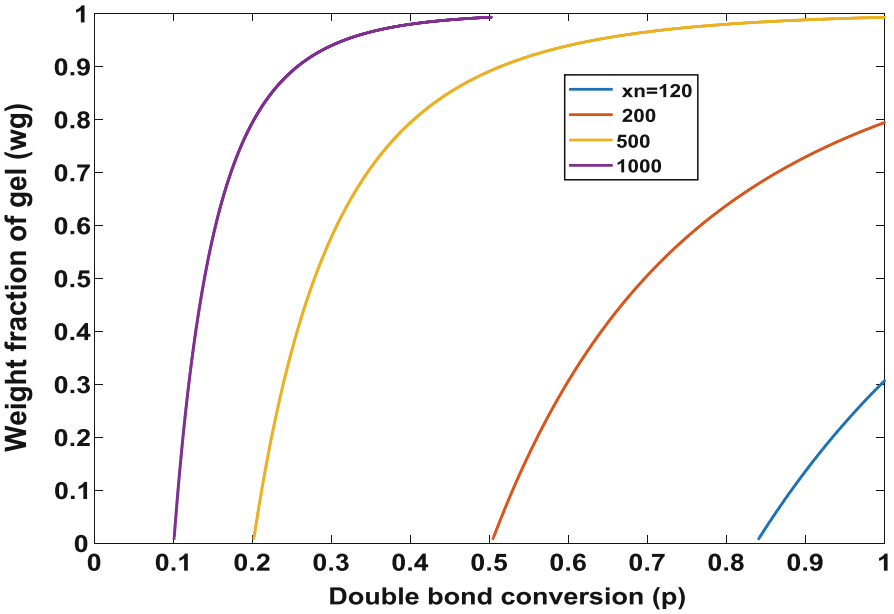

Fig. 10 Weight fraction of gel (w_g) as a function of the double bond conversion (p) in the random cross-linking of vinyl/divinyl monomers. Primary molecules of uniform length but with different values for the number-average chain length ($\bar{x}_n^* = 120$, 200, 500, and 1000) were considered in these simulations. The initial mole fraction of divinyl monomer $y_{DVM} = 0.5\%$ ($y_f \sim 1\%$) is the same in the different systems

when the formation of the primary chains and the network development is simultaneously performed, as in the case of the vinyl/multivinyl copolymerization. Indeed, the free radical copolymerization of multifunctional monomers is a kinetically controlled nonrandom process, and the network properties are critically dependent on the reaction path. It should be stressed that, in a free radical process, polymer molecules present a wide span on birth/death times. Hence, molecules are exposed to very different conditions during the reaction path, and the probability for cross-linking is not homogeneous (e.g., "primary" chains formed at the start and at the end of polymerization have unequal reaction conditions). Moreover, the vinyl groups of the different monomers involved and also the formed pendant double bonds often present distinct reactivities (see Fig. 15a). Cyclization reactions also occur to a great extent after incorporation of a multivinyl monomer (primary cyclization), increasing a lot the complexity of such cross-linking processes. These chemical effects can be magnified due to physical phenomena arising from the reaction of huge molecules with smaller polymer chains. These large molecules (see Fig. 15b) usually bear many pendant double bonds and radical centers, which can become inaccessible to further reaction due to steric hindrance.

Important deviations between predictions and measurements for vinyl/multivinyl radical copolymerizations were observed since the first works on this subject (e.g.,

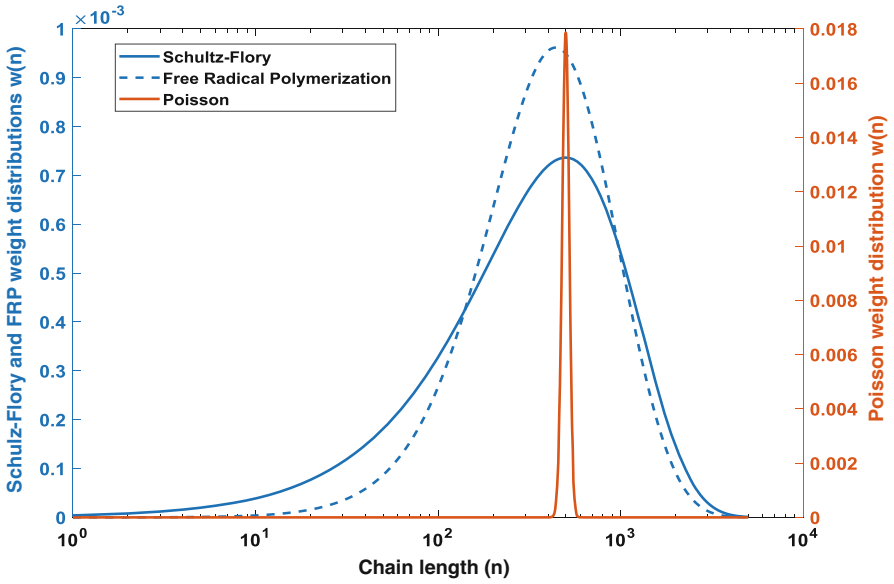

Fig. 11 Different kinds of weight chain length distributions ($w(n)$) considered in the simulations for the random cross-linking of primary chains arbitrarily distributed (see, e.g., Eq. (11)). With all the distributions the value $\bar{x}_n^* = 500$ was considered

much delayed gelation with respect to FS predictions was reported by Walling [34] when studying vinyl/divinyl copolymerization). Limitations of the statistical methods to describe nonlinear free radical polymerization, which is inherently kinetically controlled, stimulated the development of new modeling techniques. The first attempts to tackle branching by transfer to polymer are due to Beasley [40] and Bamford and Tompa [41]. In the latter approach [41], the solution of population balance equations (PBE) for polymer species was obtained through a continuous variable approximation in the Laplace domain. These ideas were at the origin of the nowadays called "method of the moments", allowing the description of kinetically controlled nonlinear polymerization systems when equal reactivity of functional groups holds.

Solution of the conservation laws for polymer species through a continuous variable approximation was considered by Zeman and Amundson [42, 43] along with several approximations to obtain a mathematically tractable problem. It is now deprecated given the use of appropriate numerical methods below described.

Kuchanov and Pis'men introduced important improvements in the kinetic theory of nonlinear polymerization in the early 1970s [44, 45]. Combination of PBE with generating functions and the solution of the resulting partial differential equations through the method of the characteristics allowed avoiding drastic approximation conditions used in precedent approaches. Avoiding the quasi-steady-state assumption for estimating radical concentrations and consideration of multiple active centers in the same molecule are decisive improvements introduced with the

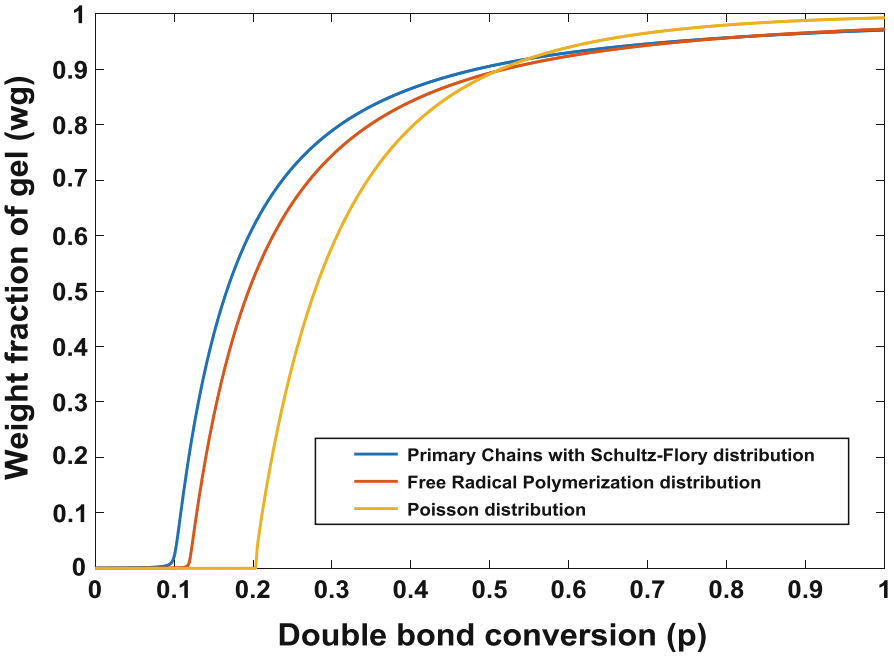

Fig. 12 Weight fraction of gel (w_g) as a function of the double bond conversion (p) in the random cross-linking of vinyl/divinyl monomers. Different kinds of weight chain length distributions for the primary chains ($w(n)$) were considered in these simulations ($\bar{x}_n^* = 500$ for all the distributions). Initial mole fraction of divinyl monomer $y_{DVM} = 0.5\%$ (y_f~1%)

Kuchanov and Pis'men works. Description of the post-gelation period is another important outcome of this kinetic theory.

In late 1980s, Tobita and Hamielec [46] introduced the pseudokinetic rate constant method to describe network formation in free radical polymerization. This method is based upon the use of moment equations, and the post-gelation period is described through the adaptation of Flory's cross-linking theory. The kinetic theory developed by Tobita and Hamielec [46] preserves the history of the generated network structure and allows a heuristic inclusion of primary and secondary cyclization. The simplicity of the numerical calculations involved makes this technique (often known as the Flory/Tobita (FT) model) very appealing for practical applications. The computations involve the instantaneous distribution of primary chains. In the framework of the pseudokinetic rate constant method, that distribution for a free radical process is described [46] by:

$$f_w(n,\theta) = \frac{n\alpha(\theta)}{(1+\alpha(\theta))^{n+1}}\left[\gamma(\theta) + 0.5\alpha(\theta)\beta(\theta)(n-1)\right] \tag{12}$$

With $\alpha(\theta) = \gamma(\theta) + \beta(\theta)$, $\beta(\theta) = k_{tc}R^{\bullet}/(k_pM)$, $\gamma(\theta) = (k_{td}R^{\bullet} + k_{fm}M + k_{fs}S)/(k_pM)$, and θ representing the birth conversion of the chains. In these equations k_p, k_{tc}, k_{td},

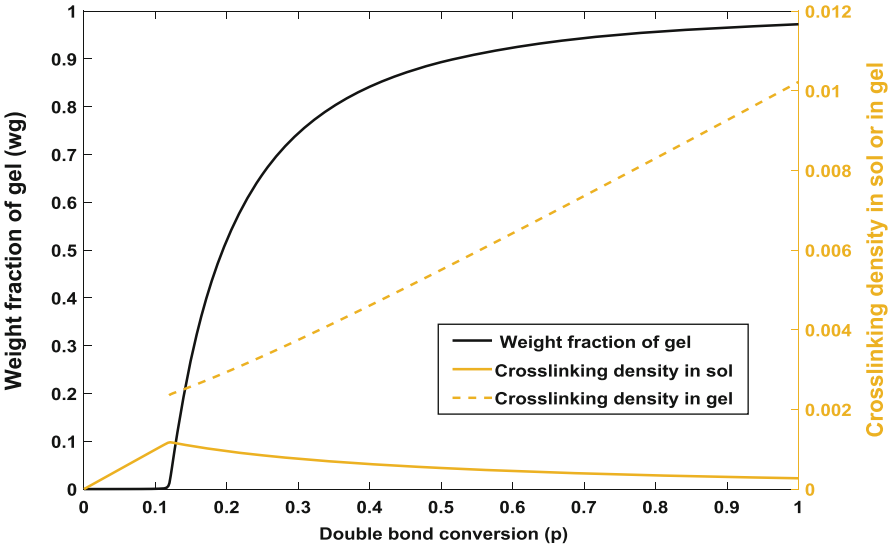

Fig. 13 Weight fraction of gel (w_g), cross-linking density of the sol (ρ'), and cross-linking density of the gel (ρ'') as function of the double bond conversion (p) in the random cross-linking of vinyl/divinyl monomers. The weight chain length distribution for the primary chains ($w(n)$) is correspondent to a polymer resulting from a free radical polymerization with $\bar{x}_n^* = 500$. Initial mole fraction of divinyl monomer $y_{DVM} = 0.5\%$ (y_f~1%)

k_{fm}, and k_{fs} stand for the pseudokinetic rate constants for propagation, termination by combination, termination by disproportionation, chain transfer to monomer, and chain transfer to solvent, respectively. On the other hand, M, $R^{\bullet}$, and S represent the total concentrations for monomer, radicals, and solvent, respectively.

The total cross-linking density at conversion ψ of the chains born at conversion θ in given by:

$$\rho(\theta,\psi) = \rho_i(\theta) + \rho_a(\theta,\psi) \tag{13}$$

The cross-linking densities and weight fraction of sol are calculated through:

$$\rho_i(\theta) = \frac{k_p^{*0}(\theta)[\bar{F}_2(\theta) - \overline{\rho}_a(\theta) - \overline{\rho}_c(\theta)]\theta}{k_p(1-\theta)} \tag{14}$$

$$\frac{\partial \rho_a(\theta,\psi)}{\partial \psi} = \frac{k_p^{*0}(\psi)[F_2(\theta) - \rho_a(\theta,\psi) - \rho_c(\theta,\psi)]}{k_p(1-\psi)} \tag{15}$$

$$w_s(\theta,\psi) = \sum_{n=1}^{\infty} f_w(n,\theta)[1 - \rho(\theta,\psi)(1 - w_s(\theta,\psi))]^n \tag{16}$$

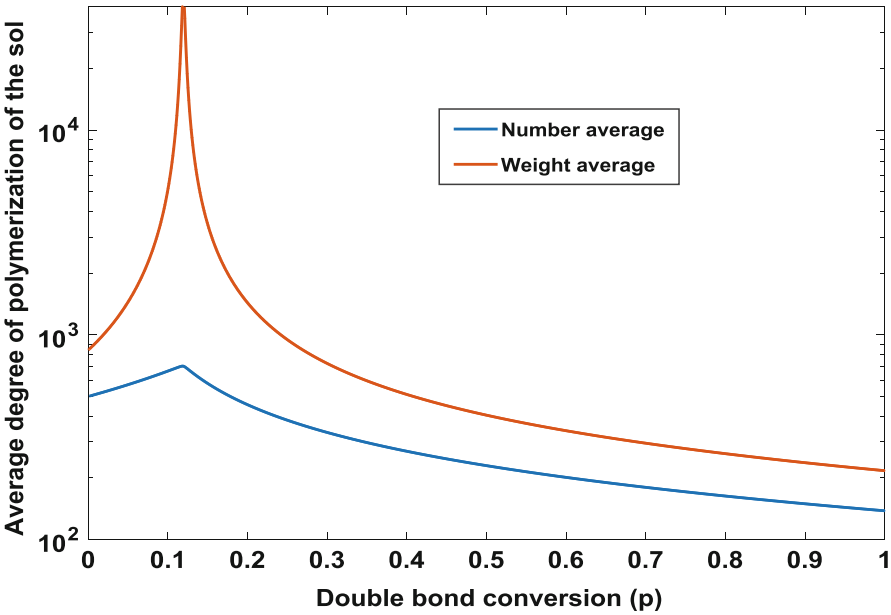

Fig. 14 Number- and weight-average chain lengths of the sol as function of the double bond conversion (p) in the random cross-linking of vinyl/divinyl monomers. The weight chain length distribution for the primary chains ($w(n)$) is correspondent to a polymer resulting from a free radical polymerization with $\bar{x}_n^* = 500$. Initial mole fraction of divinyl monomer $y_{DVM} = 0.5\%$ (y_f~1%)

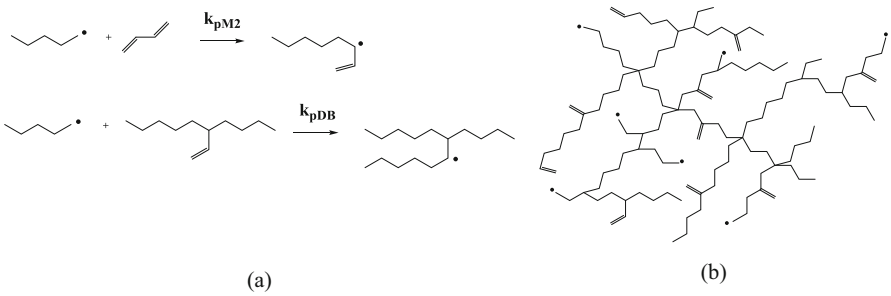

Fig. 15 (**a**) Depiction of divinyl monomer and pendant double propagation during a cross-linking process. (**b**) Large polymer molecule bearing many pendant double bonds and radical centers. Different reactivities of vinyl groups, intramolecular cyclization, and steric hindrance are examples of phenomena hampering the description of vinyl/multivinyl cross-linking systems

Details on the application of these equations and calculation methods with nonlinear free radical polymerization can be found in the original Tobita-Hamielec work [46].

The "numerical fractionation" technique was introduced by Teymour and Campbell in the 1990s [47]. This method splits the polymer population into an arbitrary

number of generations defined by a count of branching events and carries out the calculation of the moments for the polymer PBE in each generation. Transfer rules for transition of species between generations are defined. The average properties of sol and gel, as well as the chain length distribution (CLD) of the sol, can be obtained (note that the calculation of the sol CLD is not possible in the framework of the FT theory). Recently, the numerical fractionation technique was improved in order to take into account the existence in polymer population of multiradical species [48], a flaw in its original formulation. Note that modifications of the method of the moments for nonlinear FRP were also recently published [49].

This technique provides a heuristic approximation of polymer size distribution and its averages, but it is neither consistent nor convergent, in contrast with some well-based approaches, as discussed below.

5.4 Population Balances of Generating Functions

A general kinetic approach to describe different kinds of nonlinear irreversible polymerizations started to be developed in our research group in the 1990s [50]. This method stems from the ideas of Kuchanov and Pis'men [44, 45] and uses multidimensional generating functions to describe polymer populations. Through the use of a numerical approach for the solution of the resulting PBEs, several mathematical approximations inherent to alternative approaches can be avoided, namely, in nonlinear free radical polymerization processes [51]. Distinctive features of this approach comparatively to alternative methods, computation of different polymer molecular architecture parameters (CLD before and after gelation, weight fraction of gel, sequences, average radius of gyration), and its application to different kinds of polymerization systems (condensation, free radical polymerization, coordination polymerization, controlled radical polymerization) can be found elsewhere [50–61]. In a recent paper [62], the performance of four different modeling approaches (kinetic Monte Carlo, statistic/kinetic Flory/Tobita, PBE with generating functions, and PBE with numerical fractionation) was also compared in the framework of the bulk cross-linking copolymerization of vinyl/divinyl monomers.

The next case study highlights the use of population balance equations of generating functions to deal with hydrogels synthesis processes. Indeed, Eqs. (17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, and 29) depict a possible kinetic scheme describing a hydrogel synthesis (e.g., superabsorbent hydrogel) through the free radical copolymerization of an acrylic monomer (e.g., acrylic acid) with a cross-linker such as methylene bisacrylamide (MBAm, functionality $\alpha = 2$) or trimethylolpropane triacrylate (TMPTA, functionality $\alpha = 3$). In these equations, I, R_0, M_1, M_2, S, and Z stand for the initiator, primary radicals, acrylic monomer, cross-linker, solvent, and inhibitor, respectively. Polymer molecules ($P_{n,m}^{x,y}$) are described using a four-dimensional counting of radicals (n), pendant double bonds (m), polymerized acrylic units (x), and polymerized cross-linker units (y). Initiator (e.g., V50) decomposition is described through Eq. (17). Acrylic monomer, cross-

linker, and PDB initiations by primary radicals are depicted in Eqs. (18, 19, and 20). Propagations of acrylic monomer, cross-linker, and PDB with polymer radicals are shown in Eqs. (21, 22, and 23). Equations (24) and (25) represent chain transfer to acrylic monomer and to solvent, respectively. Inhibition is described through Eqs. (26) and (27) and termination by combination and by disproportionation by Eqs. (28) and (29), respectively.

$$I \xrightarrow{k_d} 2fR_0 \tag{17}$$

$$R_0 + M_1 \xrightarrow{k_{i1}} P^{1,0}_{1,0} \tag{18}$$

$$R_0 + M_2 \xrightarrow{k_{i2}} P^{0,1}_{1,\alpha-1} \tag{19}$$

$$R_0 + P^{x,y}_{n,m} \xrightarrow{k_{i3}} P^{x,y}_{n+1,m-1} \tag{20}$$

$$P^{x,y}_{n,m} + M_1 \xrightarrow{k_{p1}} P^{x+1,y}_{n,m} \tag{21}$$

$$P^{x,y}_{n,m} + M_2 \xrightarrow{k_{p2}} P^{x,y+1}_{n,m+\alpha-1} \tag{22}$$

$$P^{x,y}_{n,m} + P^{x\prime,y\prime}_{n\prime,m\prime} \xrightarrow{k_{p3}} P^{x+x\prime,y+y\prime}_{n+n\prime,m+m\prime-1} \tag{23}$$

$$P^{x,y}_{n,m} + M_1 \xrightarrow{k_{fm}} P^{x,y}_{n-1,m} + R_0 \tag{24}$$

$$P^{x,y}_{n,m} + S \xrightarrow{k_s} P^{x,y}_{n-1,m} + R_0 \tag{25}$$

$$R_0 + Z \xrightarrow{k_z} Inactive\ Products \tag{26}$$

$$P^{x,y}_{n,m} + Z \xrightarrow{k_z} P^{x,y}_{n-1,m} \tag{27}$$

$$P^{x,y}_{n,m} + P^{x\prime,y\prime}_{n\prime,m\prime} \xrightarrow{k_{tc}} P^{x+x\prime,y+y\prime}_{n+n\prime-2,m+m\prime} \tag{28}$$

$$P^{x,y}_{n,m} + P^{x\prime,y\prime}_{n\prime,m\prime} \xrightarrow{k_{td}} P^{x,y}_{n-1,m} + P^{x\prime,y\prime}_{n\prime-1,m\prime} \tag{29}$$

The general kinetic approach developed in our research group [50–61] uses generating functions (GF) of distributions instead of the related real domain functions. The GF of the distribution here used, $P^{x,y}_{n,m}$, is described by:

$$G(s_R, s_B, s_X, s_Y, t) = \sum_{n=0}^{\infty}\sum_{m=0}^{\infty}\sum_{x=0}^{\infty}\sum_{y=0}^{\infty} s_R^n s_B^m s_X^x s_Y^y P^{x,y}_{n,m}(t) \tag{30}$$

The population balance equation (PBE) for the kinetic scheme described by Eqs. (17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, and 29) in the Laplace domain is:

$$\begin{aligned}
\frac{\partial G}{\partial t} &= k_{i1}[R_0][M_1]s_X s_R + k_{i2}[R_0][M_2]s_Y s_R s_B^{\alpha-1} + k_{i3}[R_0]\left(\frac{s_R}{s_B} - 1\right)\frac{\partial G}{\partial \log s_B} \\
&+ k_{p1}[M_1](s_X - 1)\frac{\partial G}{\partial \log s_R} + k_{p2}[M_2]\left(s_Y s_B^{\alpha-1} - 1\right)\frac{\partial G}{\partial \log s_R} \\
&+ k_{p3}\left[\frac{1}{s_B}\frac{\partial G}{\partial \log s_B}\frac{\partial G}{\partial \log s_R} - [R]\frac{\partial G}{\partial \log s_B} - [B]\frac{\partial G}{\partial \log s_R}\right] \\
&+ k_{fm}[M_1]\left(\frac{1}{s_R} - 1\right)\frac{\partial G}{\partial \log s_R} + k_s[S]\left(\frac{1}{s_R} - 1\right)\frac{\partial G}{\partial \log s_R} \\
&+ k_Z[Z]\left(\frac{1}{s_R} - 1\right)\frac{\partial G}{\partial \log s_R} + k_{tc}\left[\frac{1}{s_R^2}\left(\frac{\partial G}{\partial \log s_R}\right)^2 - [R]\frac{\partial G}{\partial \log s_R}\right] \\
&+ k_{td}[R]\left(\frac{1}{s_R} - 1\right)\frac{\partial G}{\partial \log s_R}
\end{aligned} \tag{31}$$

Starting the polymerization from monomers, initiator, and solvent (and/or other non-polymeric species), the initial condition for Eq. (31) is:

$$G_{|t=0} = G_0 = 0 \tag{32}$$

Numerical inversion of the generating function can be carried out in a stable and accurate fashion through contour integration in complex plane.

This general kinetic approach is also able to deal with more complex kinetic schemes and models describing hydrogel formation, namely, intramolecular chain transfer to polymer, backbiting, or propagations with tertiary radicals [20]. These additional kinetic mechanisms should only be important at high polymerization temperature, very low cross-linker content, and high polymer concentration. Polymerization recipes for the formation of hydrogels from two vinyl monomers (e.g., acrylic acid and acrylamide) and a cross-linker can also be handled in the framework of this modeling approach [22].

Figure 16 illustrates the use of such a modeling approach with hydrogel synthesis. In Fig. 16a, it is presented the experimentally measured dynamics of gel formation in different polymerization runs concerning AA-based hydrogel production (inverse suspension processes). In Fig. 16b, it is compared the predicted and experimentally measured final weight fraction of gel for different polymerization runs concerning hydrogel synthesis. The effect of the reactivity of pendant double bonds on the predictions is here explored. In spite of the fair agreement between experimental and theoretical predictions, improvement of this modeling approach has been considered in the last few years, namely, taking into account cyclization effects [24, 63].

The prediction of the average molecular weight between cross-links ($\bar{M}_c$), an important parameter for the characterization of polymer networks, is also possible in the framework of the present modeling approach. Indeed, segments between cross-linking points can be treated as sequences of the main monomer present in the hydrogel. Methods for the calculation of sequence lengths in linear and nonlinear polymerization have been previously developed by our research group [56, 59] (see also [64] for a comprehensive overview on polymerization processes modeling, including the calculation of sequence length distributions).

5.5 Calculations with RDRP Nonlinear Polymerization

Due to the particular kinetic mechanisms involved, calculations with nonlinear RDRP systems have some numerical issues owing to their huge span of reaction times [60] and critical improvements on the above-described method based on

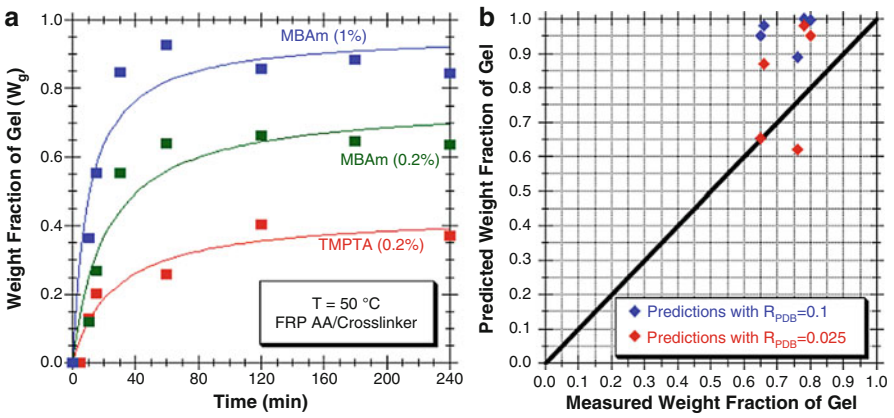

Fig. 16 (**a**) Experimentally measured dynamics of gel formation in AA-based hydrogels production. FRP polymerizations at T = 50 °C with different cross-linkers (MBAm and TMPTA) at different initial contents were considered. (**b**) Comparison of the measured and predicted final weight fraction of gel in different polymerization runs concerning the AA-based hydrogel formation. Predictions with two values for the reactivity of the pendant double bonds are presented

generating functions are being performed at the time this work is being completed. The increase of the efficiency of the numerical methods used with the solution of two-point boundary value problems involved in the calculations after gelation or in inversion of the CLD could overcome most of those issues (indeed, analysis of NMRP and ATRP nonlinear polymerization before gelation was previously performed in the framework of this approach [61, 65, 66]).

Other important tools can be found in the literature to deal with such kinds of problems, mostly based on adaptations of the method of the moments (see, e.g., [67, 68] and references therein). These calculation tools were recently explored for the development of RAFT-surface-grafted molecularly imprinted particles [25], and some useful simulations are illustrated in Fig. 17, namely, the control of the gelation process through the initial amount of RAFT agent (manipulation of the primary chains) and the CLD prediction with linear RAFT polymerization. Note that this kind of analysis is important for polymer networks and hydrogels tailoring, for design of telechelic structures, and also for RAFT-grafting processes, namely, those involving cellulose, as explored in Sect. 6.

6 Tailoring of Branched/Network Polymers and Hydrogels with RDRP Mechanisms

Reversible deactivation radical polymerization (RDRP), formerly named living radical polymerization (LRP) or controlled radical polymerization (CRP), offers the possibility to synthesize polymers with predetermined degree of polymerization and narrow molecular size distribution, tackling a major drawback of classical free radical polymerization (FRP) [69, 70]. Additionally, with RDRP, it is possible to carry out the synthesis of advanced polymer structures with tailored composition (e.g., block, statistical, gradient, or graft copolymers), architecture (e.g., linear, star, comb, network, or branched polymers), and functionality (e.g., telechelic polymers, macromonomers, multi-armed polymers, or multifunctional polymers). RDRP mechanism also provides the efficient production of molecular composites such as hybrids with inorganic and biopolymers, functional colloids, or modified surfaces [69, 70].

In this section are presented results for case studies concerning the tailoring of branched polymers, networks, and hydrogels through RAFT polymerization. The RAFT synthesis of hydrogel particles in continuous flow micro-reactor, the generation of molecularly imprinted particles with surface RAFT-grafted polymer brushes, and the RAFT-grafting of synthetic polymers in cellulose are considered as application examples. Note that, among the main RDRP mechanisms, RAFT polymerization presents some advantages due to the broad range of operation conditions and different classes of monomers that can be used [71]. This technique was also before considered in the cross-linking of different kinds of multi-olefinic monomers to generate polymer networks [72]. However, many similar applications are possible with other RDRP mechanisms, namely, ATRP and NMRP.

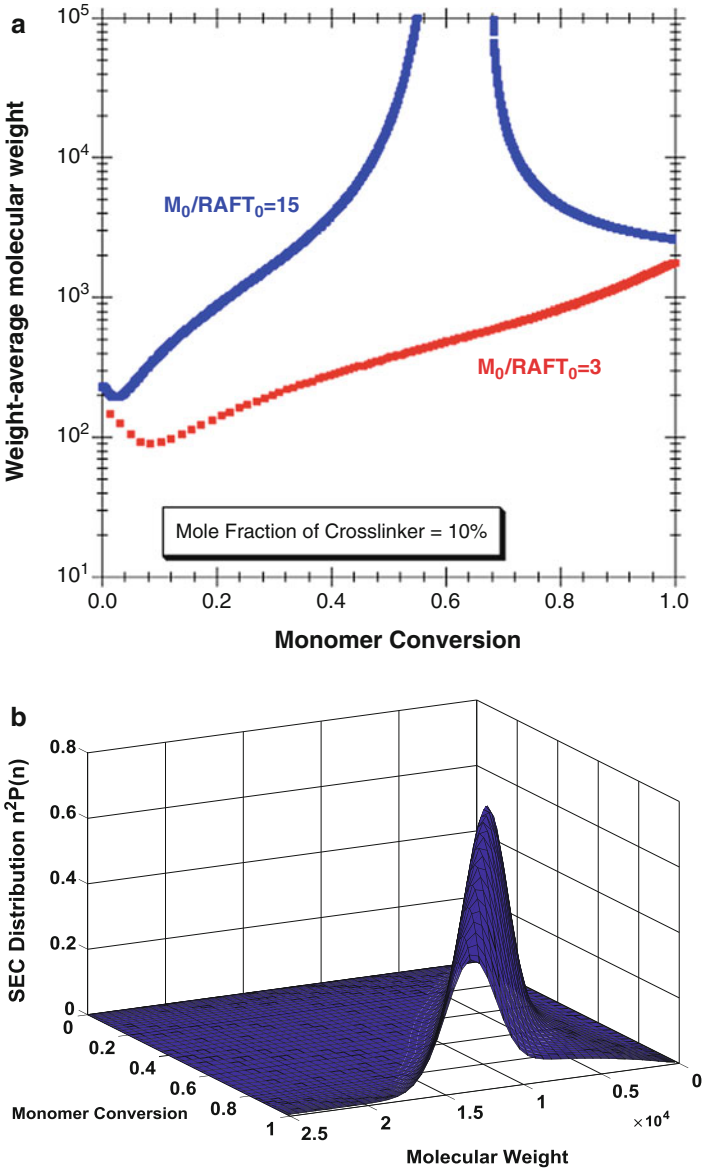

Fig. 17 (**a**) Predicted dynamics of HEMA/EGDMA hydrogel formation for processes with different initial contents of RAFT agent, showing the possibility to avoid gelation even at a high cross-linker content (see [25] for information concerning the relevant kinetic parameters). (**b**) Predicted dynamics of the CLD with the RAFT polymerization of MAA (see [68] for a general discussion concerning the influence of the kinetic mechanisms on the CLD of RAFT linear polymers, namely, the possibility for the development of bimodal distributions)

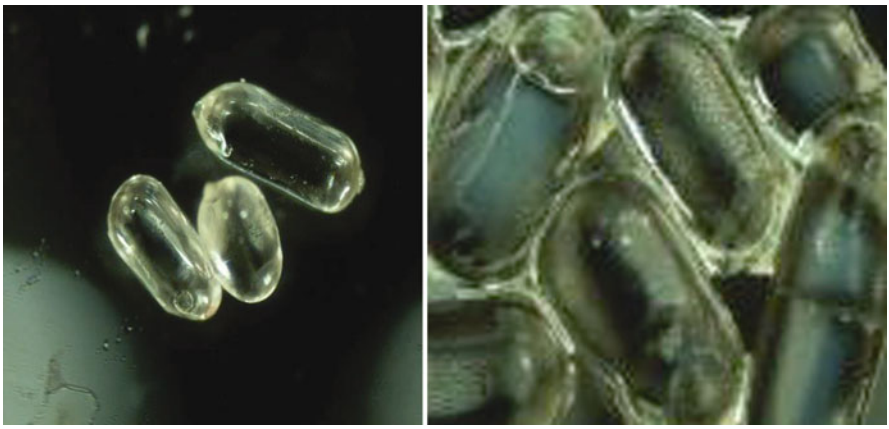

Fig. 18 Images of AA hydrogel particles synthesized in a continuous flow process. RAFT polymerization was considered to control the kinetics of the reaction and the gelation mechanism

6.1 Continuous Flow Synthesis of Hydrogel Particles with RAFT Polymerization

As pointed above, RDRP mechanisms offer the possibility for production of advanced polymer structures with tailored composition. These techniques can also be explored to try the synthesis of more homogeneous polymer networks (e.g., controlling the molecular weight between cross-links), as recently reported with RAFT polymerization [17]. Additionally, the control of the kinetics of polymerization and, eventually, the suppression of gelation (if the primary chains are sufficiently shortened) can also be conceived with these processes, as also recently described [73]. Here, it is illustrated the use of RAFT polymerization in our research to aid in the production of hydrogel particles in a continuous flow micro-reactor [74]. Indeed, it was shown that the inclusion of a RAFT agent in the developed process was important to optimize the experimental conditions in the continuous microfluidic approach. The control of the reaction kinetics, namely, the fast and exothermic reaction involving AA, was thus attained. Moreover, with RAFT polymerization, the gelation time could also be manipulated in this microfluidic approach and molecularly imprinted hydrogel particles were successfully synthesized [74]. In Fig. 18 are presented images of hydrogel particles obtained with such approach. The molecularly imprinted hydrogel particles obtained with this methodology (e.g., using 3-aminopyridine as template) also showed outstanding performance in a selective uptake process guided by the swelling of the networks [74]. These findings illustrate the use of RAFT to help the tailoring of smart hydrogels. Morphological features introduced in the hydrogels by using a microfluidic device will be further discussed in Sect. 7 of this work.

6.2 Network Polymer Particles with Surface RAFT-Grafted Functional Brushes

In the last few years, molecular architectures such as network polymer particles forming a core with surface-grafted functional polymer brushes have been explored to create materials with multiple features. A molecularly imprinted core, able to perform molecular recognition of a target molecule, bearing functional brushes grafted at the particle surface, is an example of such class of materials. The functional polymer brushes are included to provide stimulation features to the final materials and/or to modify their surface properties (e.g., hydrophilic/hydrophobic balance). A possible synthesis route of these kinds of functional materials includes two steps (see [75–80] and references therein): (i) production of network polymer particles using RAFT precipitation polymerization. A high cross-linker content is classically considered in this step if MIPs are intended. (ii) Grafting of functional polymer brushes on the core particles surface through a "grafting from" mechanism. With this goal, the RAFT groups present in the surface of the particles produced at the first stage are reactivated in this second polymerization step.

These ideas were recently explored in our research group to develop MIP particles for 5-FU (used in cancer treatment) with surface-grafted polymer brushes, aiming pH and temperature sensitivity [81]. Imprinted polymer networks based on the functional monomers MAA and HEMA, with EGDMA as cross-linker, were synthesized through RAFT precipitation polymerization in ACN. Functional brushes were afterward grafted on the surface of these MIP particles using alternatively MAA, HEMA, or NIPA as monomers. Improved sensitivity of the particles with PMAA polymer brushes to the pH of the surroundings was also proven, and a boost on drug release at 20 °C as compared to 40 °C was observed for particles with PNIPA grafted brushes [81].

Currently, we are exploring this approach to generate engineered materials for the selective uptake and release of polyphenols. These molecules are present in many vegetable extracts, and, due to their antioxidant activity, many important applications in pharmaceutics and biomedicine are being considered. In Fig. 19 are presented results concerning the batch adsorption of the polyphenol polydatin in MIP particles bearing different kinds of surface-grafted polymer brushes, namely, PMAA, PDMAEMA, and PNIPA polymers. These materials were synthesized considering the above-described RAFT process with 4VP as functional monomer for molecular imprinting and EGDMA as cross-linker. The RAFT-mediated "grafting from" mechanism was afterward considered for brushes formation at particles surface. Results presented in Fig. 19 illustrate the possibility for stimulation of the molecular recognition process through the effect of the grafted polymers (the effect of the temperature is here considered within this purpose). However, other phenomena should be considered in this analysis (e.g., the effect of pH and temperature on drugs solubility) in order to have a clear picture of these stimulated uptake/release mechanisms. Ongoing studies with these classes of materials should help to differentiate the intervenient phenomena.

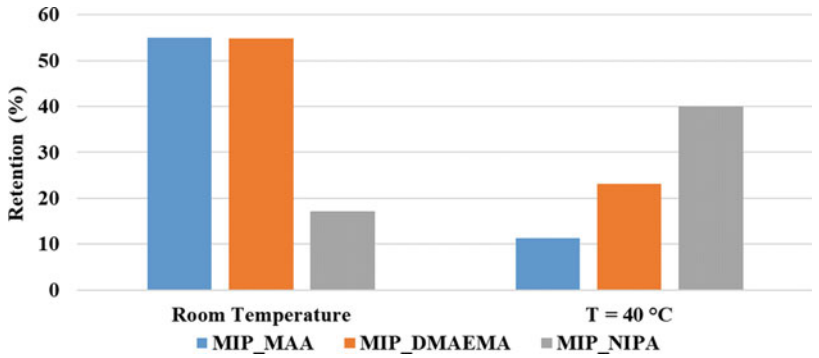

Fig. 19 Batch adsorption of polydatin in MIP particles bearing different kinds of surface-grafted polymer brushes, namely, PMAA, PDMAEMA, and PNIPA chains. Synthesis of these materials was performed through RAFT cross-linking precipitation of 4VP/EGDMA, followed by a RAFT-mediated "grafting from" process

Interestingly, the RAFT "grafting from" processes here briefly discussed have a close connection with the grafting of synthetic polymers on cellulose, as next discussed.

6.3 RAFT-Mediated Grafting of Synthetic Polymers on Cellulose

Grafting is a technique commonly used to modify the surface of many polymers. Grafting of cellulose is usually considered to improve the properties of the native natural polymer, such as water absorption capability, elasticity, hydrophilicity or hydrophobicity, adsorption features, sensitivity to external parameters (e.g., pH and temperature), antibacterial effect, etc. [82, 83]. Three main routes for grafting of cellulose are generally considered [82, 83]: (i) the "grafting from" approach consisting on the polymerization of a vinyl monomer in the presence of cellulose, whose backbone is also properly initiated for polymerization. Different methods can be used to initiate the polymerization in cellulose backbone including, e.g., the use of chemical initiators able to create radicals on cellulose or by the pre-attaching of a RAFT agent on cellulose followed by RAFT polymerization of the vinyl monomer. (ii) The "grafting to" or the "grafting through" approaches consisting on the reaction of a polymer containing reactive end groups with others present in cellulose backbone or the polymerization of a vinyl derivative of cellulose with a vinyl monomer. (iii) The "high-energy irradiation" approach where monomer and cellulose are mutually or separately irradiated.

A major challenge to be faced with cellulose grafting is due to the low solubility of this polymer in common solvents, which can hinder the reaction mechanisms involved in the grafting process. In practice, grafting of cellulose can be performed in homogeneous and heterogeneous conditions. With the homogeneous grafting, native cellulose is dissolved in a proper solvent (e.g., LiCl/DMAc), or a soluble cellulose derivative is used (e.g., hydroxyethyl cellulose or cellulose acetate). In

heterogeneous grafting, native cellulose and common solvents are directly used, and the process takes place only in the accessible regions of the polymer backbone. As a consequence of these effects, a higher grafting efficiency is ascribed to the homogeneous processes [82, 83].

In view of the ecologic/economic importance of cellulose valorization and in result of the challenges briefly described above, there is an intensive research effort on the improvement of the cellulose grafting methods and exploitation of the resulting materials (see [82–88] and references therein).

Here, we present results of our research concerning the grafting of different kinds of synthetic polymers on cellulose, using the "grafting from" approach mediated by RAFT polymerization in heterogeneous conditions. The accomplishment of this task with some of the conditions considered is also shown.

Three different kinds of cellulose were used in the studies performed, namely, cellulose fibers, cellulose microcrystalline, and cellulose filter paper (see Sect. 2). TBTGA and CPA were selected as RAFT agents containing carboxylic acid functional groups. Immobilization of RAFT agents on the cellulose substrates was performed through the esterification reaction of the acidic groups with the hydroxyl groups of cellulose, following the lines of thought reported in the literature (see [83–87] and references therein). DCC and DMAP were used as coupling agent and catalyst, respectively, for the esterification reaction. Note that, RAFT agents can be attached to cellulose via the R-group approach or the Z-group approach [83–87]. Here, the R-group approach was considered, resulting in the formation of a cellulose-supported macrochain transfer agent. Different esterification conditions were tried, namely, by combining the three types of cellulose and the two RAFT agents in three different solvents, specifically, DCM, DMF, and chloroform, following diverse alternatives also reported in the literature [83–87]. All the esterification reactions were performed at 40 °C during 3 days. Afterward, the cellulosic materials were submitted to intensive cleaning procedures [83–87] in order to remove the RAFT molecules without chemical bound to the substrates. Final purified products were dried in a vacuum oven at 40 °C.

The heterogeneous grafting of synthetic polymers on the cellulose was performed using the previously prepared cellulosic materials with attached RAFT agents and DMF as solvent for polymerization reaction. Different monomers were used in the grafting process (e.g., MAA and styrene), AIBN was selected as thermal initiator, and the same RAFT agent attached to the cellulose was considered in the polymer grafting step. All the reactions were performed at 70 °C during 24 h under stirring. The concentration of esterified cellulose in DMF was typically $P = 3$ g/L. Initial concentrations for monomer, initiator, and RAFT agent used in the grafting processes were typically $M_0 = 0.9$, $I_0 = 6 \times 10^{-3}$, and $RAFT_0 = 7.5 \times 10^{-3}$ mol/L, respectively. At the end of the reactions, the solid products and the liquid phase were separated using centrifugation. The presence of soluble polymer in the liquid phase was visually confirmed through the precipitation of a few drops in a large excess of a suitable non-solvent (such as diethyl ether or methanol). The collected liquid phase was stored at low temperature to be later analyzed, namely, using SEC. Solid materials were extensively cleaned considering several extraction processes, and

the final grafted cellulose was obtained through the drying of the products in a vacuum oven at 40 °C.

In Figs. 20 and 21 are presented some results concerning the FTIR analysis of different materials involved in the RAFT-mediated grafting of synthetic polymers on cellulose. For illustration purposes, the TBTGA-mediated grafting of PMAA on microcrystalline cellulose and the CPA-mediated grafting of PS, also on microcrystalline cellulose, are here presented. The comparison of the spectra correspondent to the synthetic polymer (PMAA or PS), the native cellulose, the cellulose substrate with esterified RAFT agent, and the final products of the grafting processes, allows to conclude that the intended cellulose-grafted materials were successfully obtained. Indeed, new FTIR assignments can be clearly identified in the grafted materials in the region 1550 to 1750 cm^{-1}. These new assignments, negligible in the native cellulose or in the correspondent substrate with attached RAFT agent, are compatible with vibrational features associated with the synthetic polymers, namely, the carbonyl C=O stretch (generically in the range 1670 to 1820 cm^{-1}) for PMAA and the aromatic C=C bending (generically in the range 1500 to 1700 cm^{-1}) for PS. In fact, the new assignments observed in the region 1550 to 1750 cm^{-1} for the cellulose-grafted materials can be closely related with vibrational peaks also appearing the spectra collected for the PMAA and PS polymers (see Figs. 20 and 21).

In Fig. 22 are presented results concerning the SEC analysis of the liquid phase correspondent to different grafting processes. These analysis were performed using DMF as eluent in order to have simultaneous solubility of different polymers, namely, PMAA and PS. Note that the same solvent was used in graft polymerization processes in order to keep the formed free polymer soluble during the reaction. These analyses provide an additional evidence for the formation of free polymer (first confirmed through the precipitation in a non-solvent, as above described) and allow to characterize the synthetic polymer population produced. With the two systems selected to illustrate these issues (PMAA and PS RAFT-grafting on cellulose), important differences can be identified with the SEC analysis of the liquid phase. Indeed, for PMAA grafting a unimodal polymer population is observed (with maximum RI intensity at around 8×10^4 molecular weight), while for PS grafting a bimodal distribution is measured (with maximum RI intensities at 4×10^3 and 8×10^4 molecular weight). Moreover, with MAA RAFT polymerization, the monomer peak is not observable in the final liquid phase, while a peak with substantial intensity is measured with S RAFT polymerization at the same conditions. The rates of consumption of the two monomers in these systems are therefore quite different. These issues highlight the important dissimilitudes possibly arising when variable RAFT-grafting systems are considered. In this context, modeling tools for RAFT polymerization, as described in Sect. 5, can provide interesting insights concerning the impact of kinetics, the operation conditions, and some mechanistic effects (e.g., the intermediated radical termination process and bimodality [68]) on the structural features of the formed polymer.

Our current research work in this field aims at the use of cellulose-grafted materials, such as those described above, for the generation of sorbents and controlled release vehicles [88], namely, molecularly imprinted polymers based on

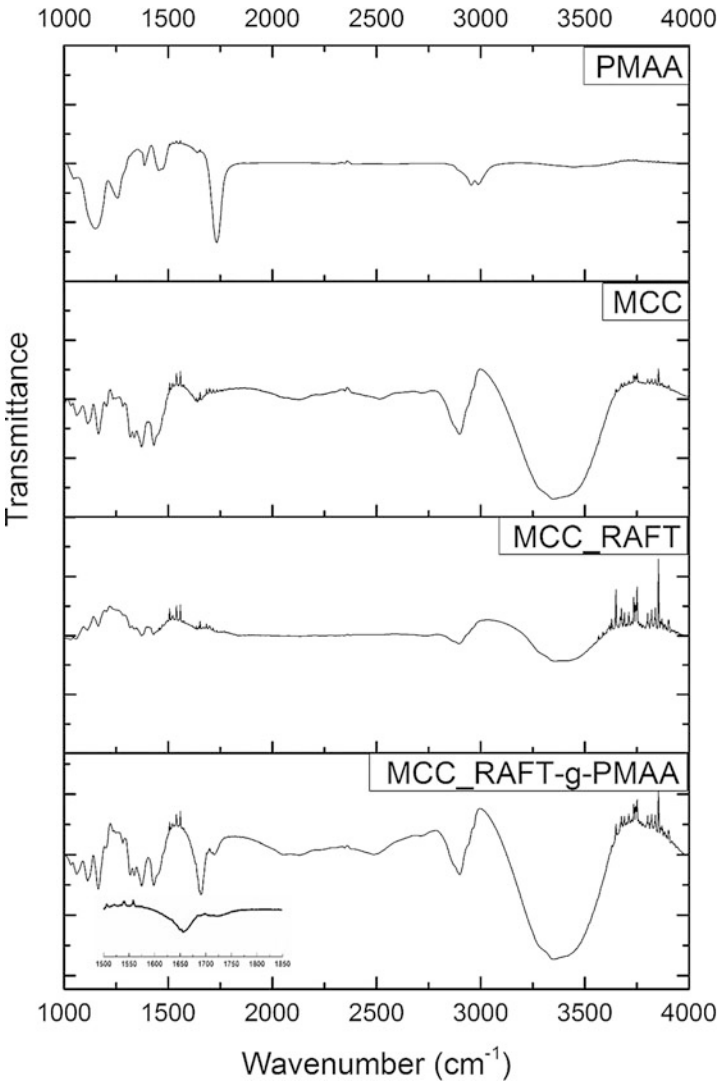

Fig. 20 FTIR spectra of different products involved in the RAFT-mediated grafting of PMAA on microcrystalline cellulose. Spectra collected for the PMAA polymer, microcrystalline cellulose (MCC), product of the esterification of microcrystalline cellulose with TBTGA (MCC_RAFT), and final product for the RAFT-grafting of PMAA on cellulose (MCC_RAFT-g-PMAA) are compared

natural macromolecules. Indeed, through the grafting of functional polymers in cellulose, improved interactions with selected template molecules can be conceived for an efficient molecular imprinting process. The ulterior generation of a polymer network, using a RAFT cross-linking mechanism with a divinyl monomer, e.g., leads (hopefully) to a MIP with molecular recognition capabilities for the template molecule, as generically depicted in Fig. 23.

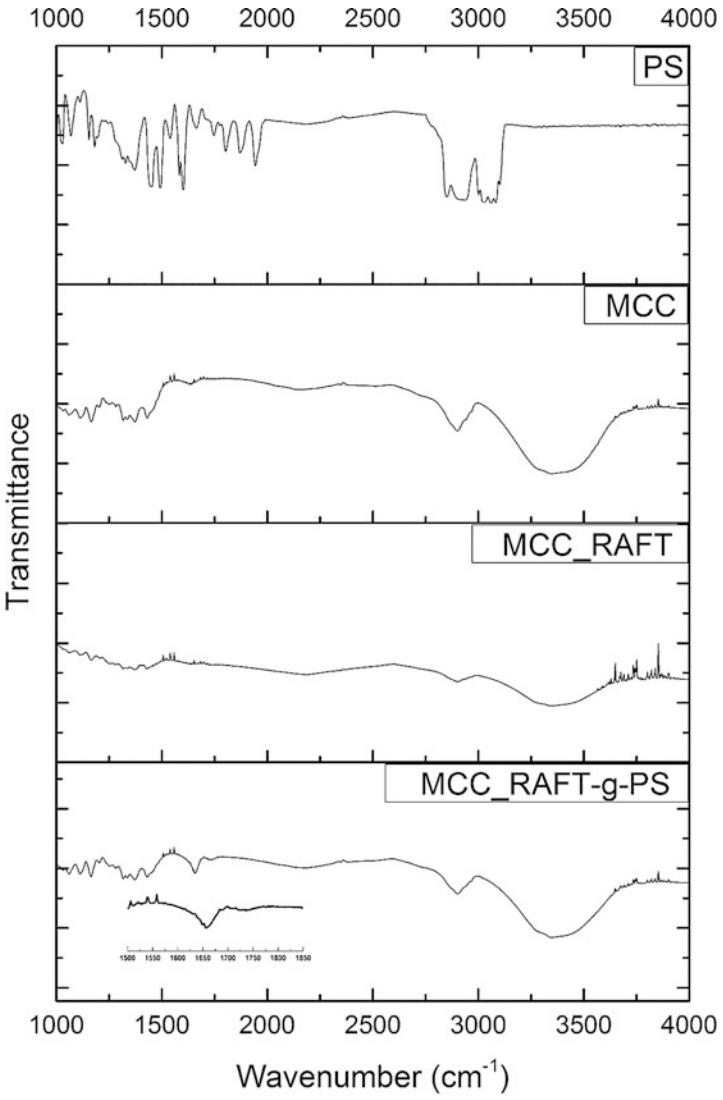

Fig. 21 FTIR spectra of different products involved in the RAFT-mediated grafting of PS on microcrystalline cellulose. Spectra collected for the PS polymer, microcrystalline cellulose (MCC), product of the esterification of microcrystalline cellulose with CPA (MCC_RAFT), and final product for the RAFT-grafting of PS on cellulose (MCC_RAFT-g-PS) are compared

However, some key aspects of the different synthesis steps are being worked out in order to achieve this final goal. Improvement of the RAFT-mediated grafting on cellulose, aiming higher efficiency and upper control on the molecular size of the synthetic functional chains, is an important issue in this context. The homogeneous RAFT-grafting process is a different approach being considered in our research. The

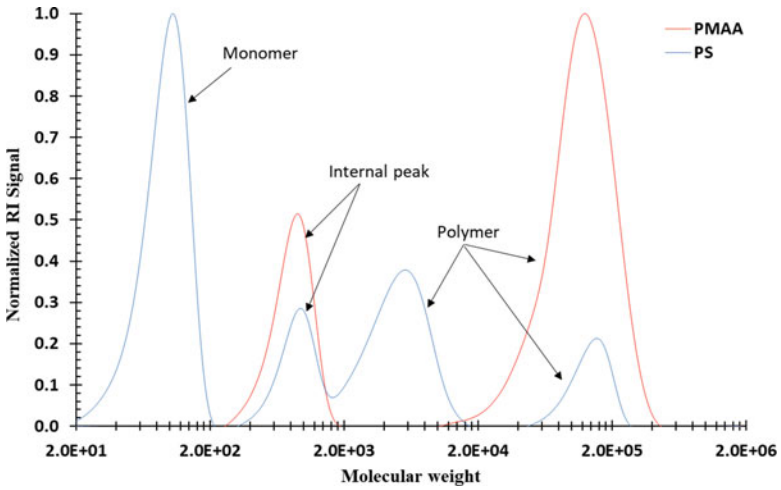

Fig. 22 SEC analysis for the final liquid-phase correspondent to the RAFT-mediated grafting of PMAA and PS on the microcrystalline cellulose. The analyses were performed using DMF as eluent at 0.4 mL/min and T = 35 °C. Polystyrene standards were used to calibrate the relation molecular weight versus elution volume

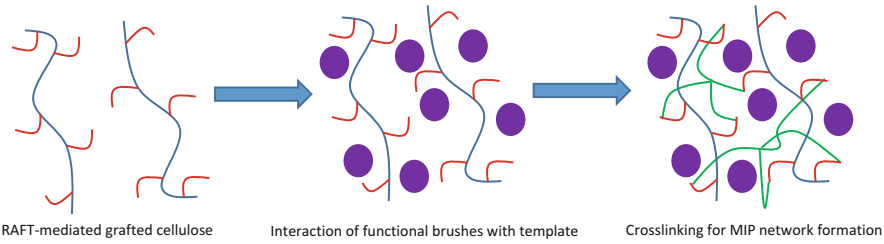

Fig. 23 Depiction of a possible molecular imprinting process based on the use of RAFT-mediated grafted cellulose and a RAFT cross-linking mechanism

favorable conditions for the formation of a polymer network in the final imprinted materials are also being investigated. A RAFT polymerization in the presence of a multifunctional vinyl monomer is being used as starting point.

7 Changing of Materials Morphology and Surface Modification

In many applications, end-use performance of polymer network-based materials and hydrogels strongly depends on mass transfer phenomena. On other hand, these transport mechanisms rely on the morphology, porosity, and surface properties, e.g., of the materials. Swelling ability and sorption/desorption capacity are examples

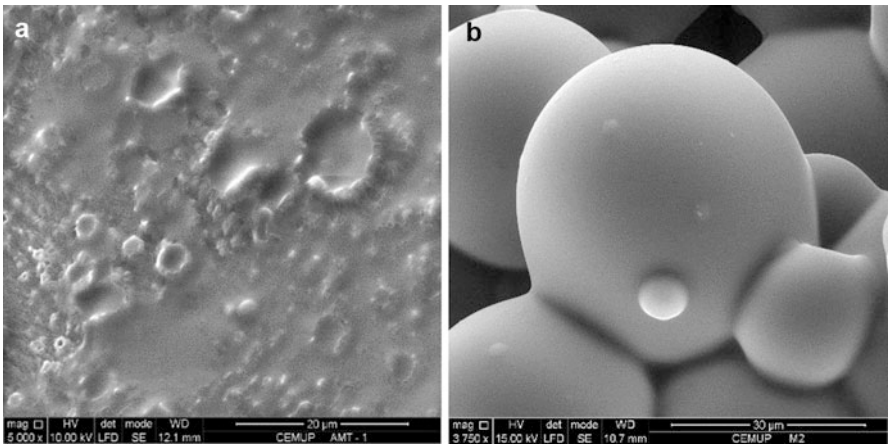

Fig. 24 SEM micrographs of AA/MBAm hydrogels produced through solution free radical polymerization process (**a**) and inverse suspension (**b**)

of important properties of polymer network materials and hydrogels that are changed by their morphology and physicochemical features.

The reaction process used in a polymerization system is an important engineering tool that can be explored to aid in the tailoring of the produced materials. Reactor type (e.g., batch, continuous, etc.) and the alternative use of solution, bulk, suspension, inverse suspension, and emulsion polymerization are examples of process variations with important impact on the morphology and final properties of polymers. Different approaches can also be used to change physicochemical characteristics of the materials, namely, their surface properties. A reaction process making use of functional groups present in the native polymers is a possible route to achieve this goal. In this section we illustrate the use of different reaction processes to change the morphology and the performance of hydrogels and SAPs. The surface modification of the materials, also impacting their applications, is highlighted with the change of the physicochemical properties of cellulose through a cross-linking process.

7.1 Polymerization Processes to Tailor Products Morphology

In Figs. 24, 25, and 26 are presented examples of different morphologies for hydrogels and polymer network products addressed in our research activities. The SEM micrograph for an AA/MBAm hydrogel produced through solution polymerization is presented in Fig. 24a. A continuous material is generally obtained in such conditions. Milling and sieving of the polymer networks is usually performed in order to enhance the mass transport properties and to control particle size. At the expense of a more complex chemistry, possibly introducing undesirable chemicals, hydrogel particles can be obtained using an inverse suspension process (see also [21, 22]). Particles in the range of few micrometers can thus be produced (see Fig. 24b),

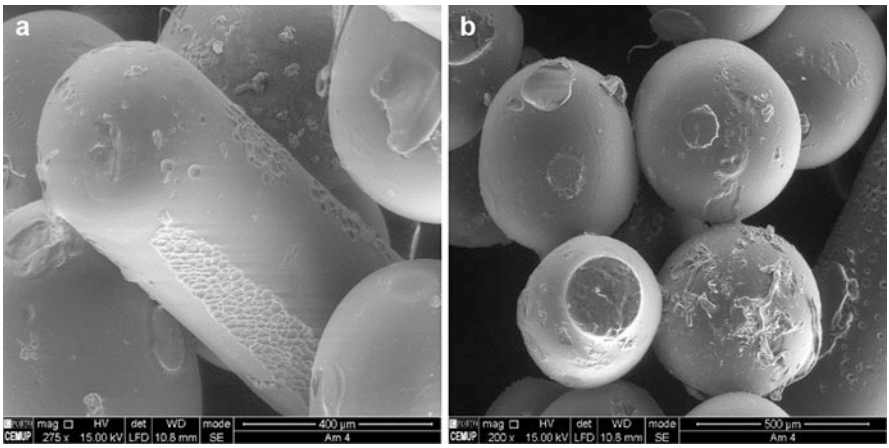

Fig. 25 SEM micrographs of AA hydrogel particles produced in a continuous flow micro-reactor. (**a**) Axial view of the cylindrical hydrogel particles. (**b**) Top view of the hydrogel particles

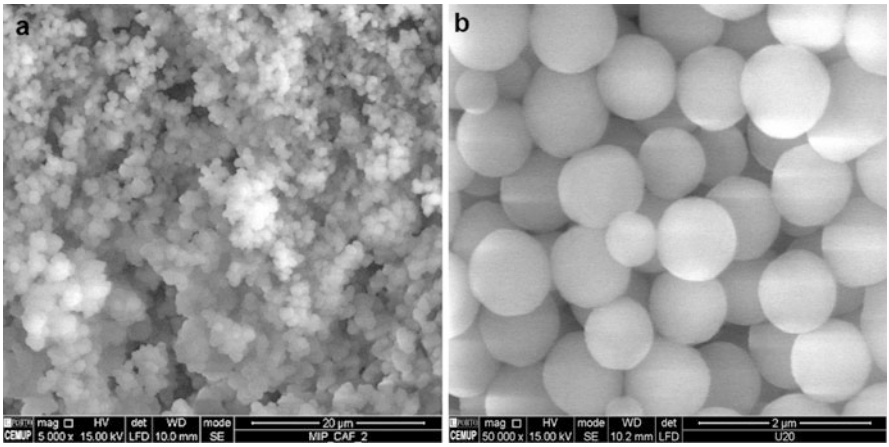

Fig. 26 (**a**) SEM micrograph of caffeine molecularly imprinted particles produced through inverse suspension. (**b**) SEM micrograph of polydatin molecularly imprinted particles produced through precipitation polymerization

and the process conditions (continuous to disperse mass ratios, surfactant concentration, etc.) can be considered in order to manipulate the particle size. Fast swelling of such materials is usually observed, as previously shown in Sect. 3 of this work.

Operation in microfluidic reactors [74] is a possible route to produce hydrogel particles, avoiding the use of some chemicals inherent to inverse suspension (intensive cleaning of the materials is usually needed with this approach) and providing additional possibilities to control the size and the shape of the products. Examples of such kinds of morphologies are presented in Fig. 25. The huge swelling capacity of

these hydrogel particles triggered by a molecular recognition mechanism put into evidence the distinct features that can be obtained with this class of materials [74].

Molecular recognition capabilities and imprinting efficiency of molecularly imprinted polymers (see also Sect. 8 of this work) are strongly dependent on their synthesis process and final product morphology (see also [81, 89] and references therein). In Fig. 26 are presented SEM images correspondent to two different products obtained in this context by using differentiated polymerization approaches. Figure 26a is correspondent to a caffeine MIP produced through inverse suspension [89]. High performance of such particles, namely, as chromatographic packings, was observed [89]. Note that a kind of surface molecular imprinting process, guided by the inverse suspension conditions, should be an important contribution for the molecular recognition capabilities of these particles. SEM images for a polydatin MIP produced through precipitation polymerization are presented in Fig. 26b. Individual particles of very small size (in the microscale or nanoscale if desired) can be produced with this technique, which enhances the mass transfer mechanisms. Moreover, the surface grafting of polymer brushes in these particles can be readily performed (e.g., using a RAFT-mediated process). Introduction of stimuli-responsive features and surface modification are possible advantages of such approach [81].

7.2 Cross-Linking of Cellulose to Modify Physicochemical Properties

Recently, many studies addressed the synthetic modification of cellulose to improve physicochemical properties, namely, the dispersion capacity, hydrophobicity, and biocompatibility (see [90] and references therein). Chemical cross-linking of cellulose is pointed out as a facile route to improve the adsorption capabilities and hydration of the native polymer in consequence of the change of the surface area and related chemical properties [90]. Considering these possibilities, and in view of the development of cellulose-based adsorbents for polyphenols, we illustrate here simple studies concerning the cross-linking of cellulose with epichlorohydrin and the assessment of the resulting materials. The sorption capabilities of the generated cellulose-based materials in comparison with synthetic MIPs specifically designed to target polyphenols are also briefly discussed.

Cross-linking of cellulose with epichlorohydrin was performed following the procedures reported in the literature [90]. In a typical experiment, 2 g of cellulose fibers (medium, cotton linters) was heated under stirring in 16 mL of a 2 M NaOH aqueous solution at 80 °C during 3 h. Argon was used to provide an inert atmosphere in the vessel. Afterward, 1 mL of epichlorohydrin was dropwise added to the mixture, which was kept at 80 °C under stirring during 12 h to promote the cross-linking process. Finally, the products were neutralized with an HCl solution (1 M), and several cleaning steps were performed to isolate the cross-linked cellulose, as described in the literature [90].

A simple evidence for the modification of the physicochemical properties of the cellulose was obtained by submitting the native and cross-linked materials to the alkali/urea method for dissolution in aqueous systems, with cycles of cooling and thawing [7–9], as described in Sect. 3. In Fig. 27 are presented images of the resulting mixtures, showing the total dissolution of the native cellulose and the total insolubility of the modified polymer.

In Fig. 28 are presented results for the SPE retention of polydatin in the native cellulose fibers, in the modified fibers, and in an inverse suspension synthesized polydatin-molecularly imprinted polymer based on 4VP/EGDMA. A 0.02 mM polydatin solution in ACN/MeOH was used to carry out these studies. Measurements here performed put into evidence the superior performance of the specifically designed MIP for the polyphenol uptake comparatively to the cellulose-based

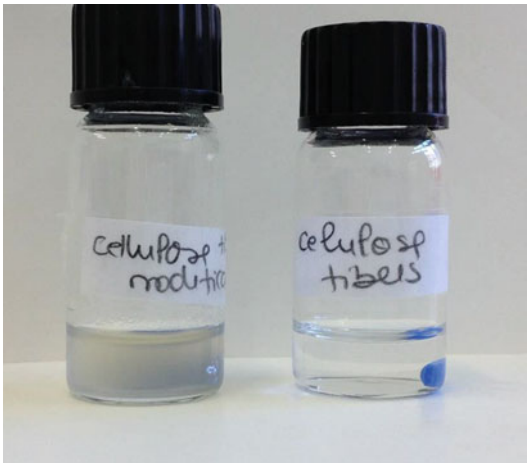

Fig. 27 Images for the mixtures resulting from the dissolution procedures applied to the epichlorohydrin-modified cellulose (left) and the unmodified cellulose (right). Following the alkali/urea method for dissolution of cellulose in aqueous systems with cycles of cooling and thawing, total dissolution was observed for the native cellulose, but the modified polymer remained totally insoluble

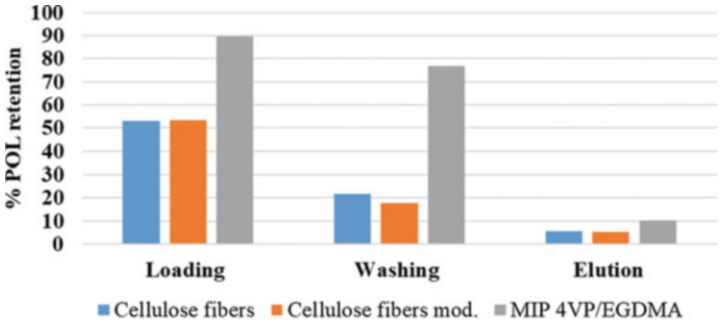

Fig. 28 Results for the SPE retention of polydatin in different sorbents, namely, the native cellulose fibers, the modified fibers, and in an inverse suspension synthesized polydatin-molecularly imprinted polymer based on 4VP/EGDMA. These testing conditions concern the loading of a 0.02 mM polydatin solution in ACN/MeOH (10/1), washing with the same eluent and elution with pure MeOH

sorbents. However, a relatively high retention is observed with both cellulose adsorbents (c.a. 50% retention). These results indicate that the benefits of cellulose modification on the polydatin retention capability are negligible, but some advantages on the use of the cross-linked cellulose can be conceived. Indeed, when the use of these cellulose polymers in continuous adsorption processes is sought, namely, as packing materials, the hardening and insolubility achieved with the cross-linking process are useful (e.g., avoiding the backpressure problem observed with some packing materials). The application of the modified cellulose as packing materials for polyphenol retention is currently being addressed in our research group.

Note that only a simple modification of cellulose for polyphenols adsorption was here discussed but more complex approaches can be considered within this purpose. Indeed, through the grafting of functional brushes on cellulose (e.g., using the RAFT-mediated processes discussed in Sect. 6), more specific interactions between the polyphenols and the adsorbent can in principle be created (e.g., including acidic or amine functional groups in the brushes). Additionally, the formation of a MIP network based on cellulose can also be thought, as depicted in Fig. 23, Sect. 6. In a different perspective, the analysis of the adsorption of polyphenols in cellulose is an important issue nowadays to understand the bioavailability of these antioxidant molecules, their metabolism, and pharmacokinetics [91].

8 Molecularly Imprinted and Non-imprinted Vehicles for Uptake and Controlled Release

Many polymer networks are designed to perform as vehicles for uptake and controlled release of target molecules. Here we illustrate the use of two very different systems within this general purpose. Molecularly imprinted polymers (MIPs), classically synthesized with a very large content of cross-linker to assure geometrical stability of the binding sites, and hydrogels, lightly cross-linked materials designed to allow swelling/shrinking induced mechanisms, are considered to highlight these differences.

8.1 Molecular Recognition with Molecularly Imprinted Polymers

Molecularly imprinted polymers (MIPs) play the role of artificial antibodies and are based on the creation in a polymer network of tailor-made cavities having high specificity and affinity with respect to a specific target molecule [92–94]. Nowadays, an intense research activity on MIPs is observed due to the important applications of these materials in many kinds of separations, solid-phase extraction, sensors, catalysis, and many biological processes (e.g., controlled drug delivery) [94, 95].

Classically, MIPs are produced with a very large content of a cross-linker plus a functional monomer, able to create specific interactions with the target molecule. After network formation, the binding sites formed should preserve the geometrical stability in order to uptake and release the target molecule in several cycles. Thus,

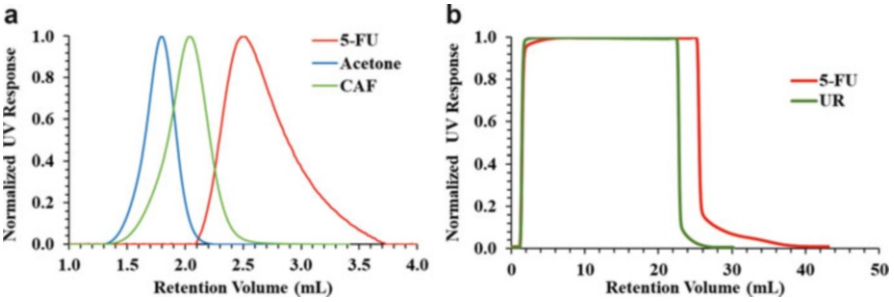

Fig. 29 Application of 5-FU MIP particles based on MAA/EGDMA, obtained by inverse suspension, as column packing for continuous adsorption/desorption processes: (**a**) chromatographic elution of 5-FU, caffeine, and acetone using ACN as eluent. (**b**) Uptake and release of 5-FU and UR in a frontal analysis process. A 50/4.6 length/diameter mm/mm column was used in these experiments

swelling is (in principle) almost unwanted with MIPs. However, performance of MIPs is affected by several factors concerning their preparation (chemical composition, polymerization process, morphology, etc.) and also their application (e.g., hydrophilic/hydrophobic interactions with the solvents considered). Therefore, there is plenty of room to develop new MIPs and improve their performance. MIPs for aminopyridines with swelling-induced molecular recognition [74], molecular imprinting of caffeine, and 5-FU in different kinds of particles (e.g., with inverse suspension or precipitation polymerization) [89] and RAFT-surface grafting of functional brushes in MIP particles to improve stimulation [81] are some recent activities of our research group in this area. Development of MIPs to address the uptake/release of polyphenols is another ongoing task, as before described in Sect. 7 of this work.

In Fig. 29 is illustrated a potential use of MIP particles in molecular recognition processes. 5-FU MIP particles based on MAA/EGDMA were synthesized by an inverse suspension process and packed in a small GPC column for assessment in continuous processes applications. Clear molecular recognition capabilities of the produced materials for 5-FU are evidenced in the chromatographic elution test (acetone and caffeine were considered as alternative molecules) and also in the frontal analysis experiment where the structural analogue uracil was also used. Note that ACN was used as eluent in these experiments and very different results can be obtained if other eluent is considered, such as water, due, e.g., to the role of the hydrophobic interactions [89]. Controlled swelling and morphological features of these particles are also important issues to avoid backpressure problems with continuous operation.

8.2 Swelling-Induced Controlled Release: A Case Study with Cellulose Hydrogels

Hydrogels are appealing controlled release vehicles due to their ability to control the transport of molecules in the network matrix. Additionally, as a consequence of their

high swelling capacity, biocompatibility, biodegradability, and biological functions, hydrogels based on natural polysaccharides, like cellulose, find many interesting applications in biomedicine, pharmacy, cosmetics, or food industry [5–9]. However, in order to design materials for accurate controlled release processes, the specific mechanisms intervenient in the transport of the target molecules inside the hydrogels should be known. Thus, important mathematical tools were developed in this research field in order to understand and develop tailored controlled release vehicles based on hydrogels [96–102].

For non-swellable devices, in the form of a thin polymer film, where the one-dimensional release of a solute from a slab applies, the following solution of the second Fick's law describes the amount $M(t)$ released along at time t:

$$\frac{M(t)}{M_\infty} = 1 - \sum_{n=0}^{\infty} \frac{8}{(2n+1)^2\pi^2} \exp\left[-\frac{D(2n+1)^2\pi^2}{L^2}t\right] \tag{33}$$

M_∞ in Eq. 33 is the amount of solute released when time approaches infinity and D the diffusion coefficient of the solute in the polymer matrix. A slab of thickness L, initially at uniform constant concentration of solute C_0 and which surfaces are kept along the time at constant concentration C_S, is here considered as model diffusion system [96, 101]. Solutions for analogue problems with cylinders or spheres can be obtained [96, 101]. Note that the solution presented in Eq. (33), as well as the equivalent solutions for cylinders and spheres (see [96, 101] for details on the solutions for these geometries), is independent of C_0 (which defines the initial condition) and C_S (which sets the boundary conditions at the slab surfaces).

In order to simplify the interpretation of experimental data obtained for the drug release in different devices, the empirical equation below was introduced by Ritger and Peppas [96]:

$$\frac{M(t)}{M_\infty} = kt^n \tag{34}$$

The above relation was shown to hold for the initial 60% of the release curve and to be valid for non-swellable vehicles with different geometries. The use of this equation was also extended to swelling-controlled release systems, namely, those prepared by incorporation of a drug in a hydrophilic glassy polymer, as long as a moderate equilibrium swelling ratio is observed (not higher than 1.33) [97].

The picture becomes much more complex with swellable-controlled release devices because the penetrant component (generally water) as soon as it gets into the polymer network also modifies its rate of drug release. Coupling of diffusion with macromolecular relaxation is generally observed and the transport of the drug outward the hydrogels is affected by the magnitude of these two phenomena. Modeling of such processes belongs to the general class of problems known as moving boundary problems or Stefan-Neumann problems (see [97–99] and Chap. 13 in Ref. [101]) and only numerical solutions are usually possible (see also [102] for a comprehensive view of hydrogels modeling). However, a heuristic model

developed by Peppas and collaborators [98] can fit the experimental data and thus allows the estimation of the contribution of the diffusion and relaxation mechanisms for anomalous drug release. It should also be stressed that phase equilibria and convective transport play an important role on drug uptake and release mechanisms in hydrogels, namely, at the boundary layer between the liquid phase and the insoluble polymer phase. Mass balance equations for the two phases should be solved in these circumstances, as depicted below for a hydrogel slab immersed in a liquid:

Hydrogel phase:

$$\frac{\partial C_A^H}{\partial t} = D_A \frac{\partial^2 C_A^H}{\partial x^2} \tag{35}$$

With initial and boundary conditions:

$$t = 0, -L/2 \le x \le L/2, C_A^H = C_{A0}^H$$

$$t > 0, x = \pm L/2, -D_A \left.\frac{\partial C_A^H}{\partial x}\right|_{x=\pm L/2} = k_c\left(C_A^{L*} - C_A^L\right) \tag{36}$$

Liquid phase:

$$\frac{dC_A^L}{dt} = k_c\left(C_A^{L*} - C_A^L\right) a_v \frac{V_H}{V_L}$$

$$t = 0, C_A^L = C_{A0}^L \tag{37}$$

In these equations, C_A^H and C_A^L represent the concentration of the drug in the hydrogel and liquid phase, respectively, L is the thickness of the slab, k_c the convective mass transfer coefficient between the two phases, and a_v is the surface area per unit of volume in the hydrogel. V_H and V_L represent the volumes of hydrogel and liquid in the system, and it is considered that the partition of the drug between the two phases is expressed by the coefficient $K = \frac{C_A^H\big|_{x=\pm L/2}}{C_A^{L*}}$. Thus, C_A^{L*} represents the concentration of the drug in the liquid phase that is in equilibrium with the surfaces of the hydrogel slab.

In Figs. 30 and 31 we present the analysis of experimental data for the uptake and release of the polyphenol polydatin in cellulose-based hydrogels (their synthesis with epichlorohydrin was presented in Sect. 3). Note that the understanding of the positive and negative biomedical interactions of polyphenols with cellulose [91] is being addressed in the scientific community because cellulose-based materials are potential vehicles for their controlled release [9].

The fraction of mass uptake during the impregnation of two different cellulose-based hydrogels with polydatin is presented in Fig. 30. Initially dried hydrogels were swelled in 5% ethanol aqueous solution containing polydatin at the concentration of 2 mM. Ethanol was used in order to provide the total solubility of polydatin in the

liquid phase. Uptake history data for the first stage were fitted to the power law $M(t)/M_\infty = kt^n$. Diffusion exponents close to $n = 0.56$ were obtained for both hydrogels, thus suggesting an anomalous (non-Fickian) transport mechanisms [9, 96–98]. Coupling of diffusion and relaxation phenomena are therefore intervenient in these hydrogel loading processes.

Loaded hydrogels were thereafter dried at 40 °C and submitted to a release process for polydatin in a 5% ethanol aqueous solution. Concentration of polydatin in the liquid phase was measured for different time instants using UV absorption. Figure 31 shows the analysis of experimental data up to 60% release fraction. A diffusion exponent close to $n = 1$ was estimated with HCEL-8, indicating a Case II transport drug release mechanism [9, 96–98] and very close to a zero-order device under these conditions (constant release rate). The diffusion exponent calculated for HCEL-5 was n~0.88; it is also compatible with an anomalous transport mechanism, coupling diffusion and relaxation, but with prevalence of the latter, as further discussed in the next section where the release of polydatin from hydrogels impregnated at supercritical conditions is analyzed.

9 Supercritical Fluid Technology Applications with Polymer Networks and Hydrogels

9.1 Overview

One of the largest potential applications of supercritical fluid technology is the area of polymer synthesis and polymer processing (see [103], Chap. 5, concerning the polymer-supercritical fluid calculations). Indeed, it is well known that supercritical fluids have properties between those of a gas and a liquid, allowing, e.g., to compromise between high diffusion rates and high solubility in many complex mixtures. Based on these and many other advantages (e.g.," green technology," low toxicity in food, pharmaceutical, biomedical applications, etc.), supercritical fluid technology has been used in many different areas, namely, the impregnation of polymers [104, 105], microencapsulation [106], hydrogels tailoring for different applications [107–110], and diverse ranges of polymer synthesis [103, 111–113] including also polymer networks and hydrogels (see [17] and references therein).

In any supercritical fluid technology application, knowledge on the thermodynamic parameters impacting the phase behavior of the mixtures, namely, their solubility levels, is of utmost importance to understand and design the desired extraction, impregnation, separation, or reaction processes. In this context, equations of state (EOS) are especially useful to perform pressure-volume-temperature (PVT) calculations for the pure components and multicomponent mixtures. Peng-Robinson cubic EOS Eq. (38) is often used within this purpose for small molecules:

$$P = \frac{RT}{v-b} - \frac{a(T)}{v(v+b)+b(v-b)} \tag{38}$$

Above, v represents the molar volume of the fluid and a and b model parameters. Combining rules should be used to define these parameters when mixtures are used [103]. However, when huge polymer molecules are involved, these kinds of EOS are no longer valid, and alternative models must be used. The Sanchez-Lacombe EOS is very popular for polymer-supercritical calculations, being represented by:

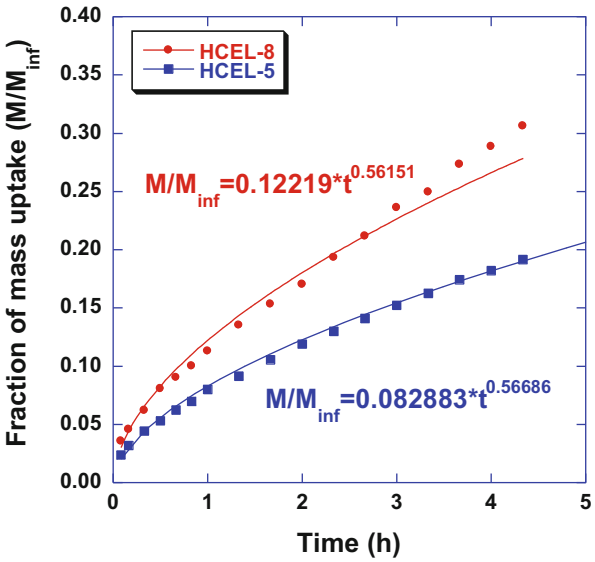

Fig. 30 Initial stage for the fraction of mass uptake, $M(t)/M_\infty$, during the swelling of two initially dried cellulose-based hydrogels in a 5% ethanol aqueous solution containing polydatin at a concentration of 2 mM. Dried hydrogels in the form of single cylinder pieces with typical diameter × thickness = 10 × 3 mm × mm were used. The equilibrium ("infinite") time was 6 days

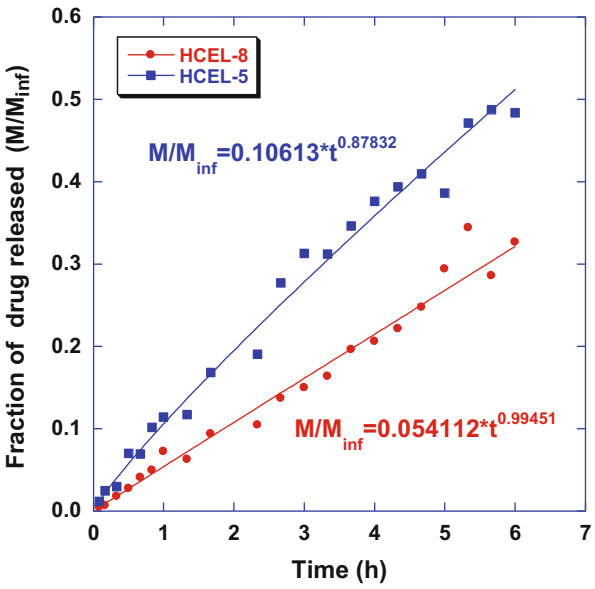

Fig. 31 Initial stage for the fraction of drug (polydatin) release, $M(t)/M_\infty$, from two initially dried cellulose-based hydrogels when poured into a 5% ethanol aqueous solution. The equilibrium ("infinite") release time was 6 days

$$\tilde{\rho}^2 + \tilde{P} + \tilde{T}\left[\ln(1-\tilde{\rho}) - \left(1 - \frac{1}{r}\right)\tilde{\rho}\right] = 0 \tag{39}$$

where $\tilde{P}$,$\tilde{T}$, and $\tilde{\rho} = 1/\tilde{v}$ represent the reduced pressure, temperature, and density, respectively. Definition of model parameters (r and other quantities) as well as combining rules for mixtures can be found elsewhere (see [103] and references therein).

9.2 A Case Study with the Impregnation of Polyphenols in Cellulose-Based Hydrogels

These tools are being used in our research to develop process conditions for different kinds of polymer synthesis and manipulation, namely, networks and hydrogels (e.g., molecular imprinting), cellulose-synthetic hybrids (RAFT-grafting, interpenetrating polymer networks), and materials impregnation for drug delivery. The upload of polydatin in cellulose-based hydrogels using supercritical CO_2 will be here considered to illustrate these kinds of applications.

Figure 32 shows an image of a cellulose hydrogel piece after impregnation with polydatin in supercritical CO_2 at T = 40 °C and P = 170 bar during 1 h. A 5% ethanol aqueous solution containing polydatin at the concentration of 2 mM was also included in the supercritical loading process. The speedup of the impregnation process with sc-CO_2 is one of the advantages introduced due to the higher diffusivity of the molecules in the network matrix, namely, the relatively high size polyphenol template used. Indeed, 1 hour was here used and around 6 days in the swelling process described in Sect. 8.

After impregnation with $ScCO_2$, hydrogels were dried at 40 °C in vacuum oven and submitted to a release process for polydatin in a 5% ethanol aqueous solution, as

Fig. 32 Image of a cellulose hydrogel piece after impregnation with polydatin in supercritical CO_2 at T = 40 °C and P = 170 bar during 1 h. A 5% ethanol aqueous solution containing polydatin at the concentration of 2 mM was also included in the supercritical loading process

before. Results for the dynamics of drug release are presented in Fig. 33, and, in spite of some scattering in the experimental data, steady state seems to be approached at around 60 h of release time.

Analysis of the period up to the first 60% drug release is performed in Fig. 34 where the fitting of the experimental data to the heuristic models $M(t)/M_\infty = kt^n$ and $M(t)/M_\infty = k_1 t^m + k_2 t^{2m}$ is also included. The latter model was developed to quantify

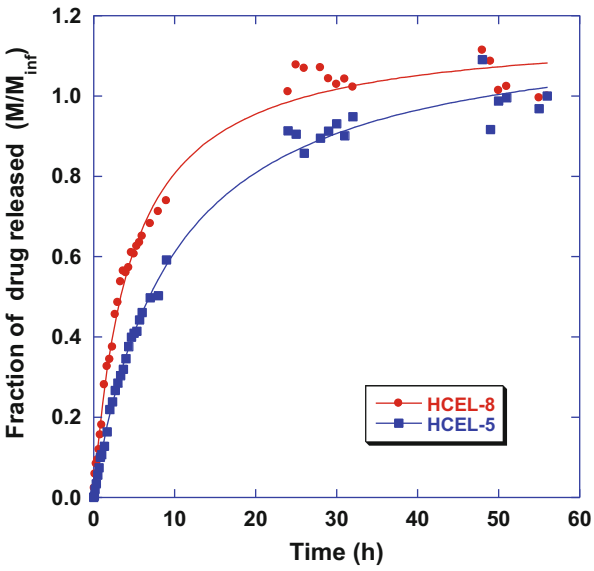

Fig. 33 Fraction of drug (polydatin) release, $M(t)/M_\infty$, from two initially dried cellulose-based hydrogels after pouring into a 5% ethanol aqueous solution. Impregnation of the polydatin in the hydrogels was previously performed in supercritical CO_2 at T = 40 °C and P = 170 bar during 1 h

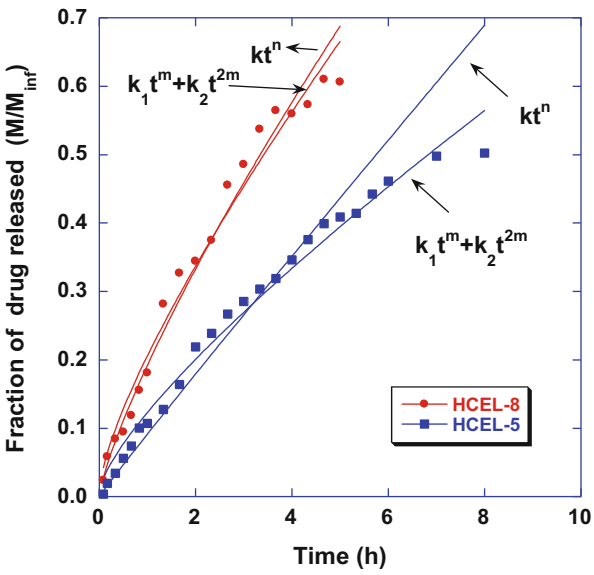

Fig. 34 Fraction of drug (polydatin) release, $M(t)/M_\infty$, from two initially dried cellulose-based hydrogels after pouring into a 5% ethanol aqueous solution. The period up to 60% drug release is here analyzed. Impregnation of the polydatin in the hydrogels was previously performed in supercritical CO_2 at T = 40 °C and P = 170 bar during 1 h

the relative contribution of the coupled diffusion and relaxation mechanisms, knowing the equation exponent (m) through the aspect ratio of the release device [98].

Considering the dimensions of the dried hydrogel pieces, the value $m = 0.43$ was used in our analysis [98]. With the base model, the diffusion exponents calculated for HCEL-8 and HCEL-5 are n~0.79 and n~0.97, respectively, putting into evidence again the anomalous transport mechanism involved. Discrimination of the diffusion and relaxation mechanisms can be estimated through the calculation of the parameters k_1 and k_2 in the second model. The following values were obtained: $k_1 = 0.078$ $h^{-0.43}$ and $k_2 = 0.128$ $h^{-0.86}$ with HCEL-8 and $k_1 = 0.048$ $h^{-0.43}$ and $k_2 = 0.075$ $h^{-0.86}$ with HCEL-5. Using these values, the Fickian release fraction [98] estimated for two cellulose-based hydrogels was obtained, and the results are presented in Fig. 35. After around 30 min release time, the polydatin liberation process starts to be clearly dominated by the relaxation of the polymer network for both hydrogels.

Results just presented show the usefulness of some simple tools to develop cellulose-based hydrogels (eventually including synthetic grafted chains) with tunable relaxation properties for drug release.

10 Conclusions

Polymer networks and hydrogels are "products-by-process" materials, and therefore their structure and final properties are defined during the synthesis process. Calculation tools with different degrees of complexity (and applicability), with the purpose of aiding the design of processes for the production of such materials, were presented

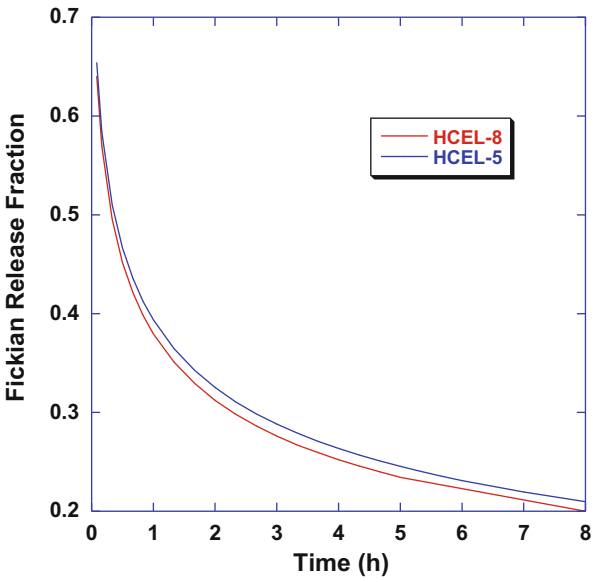

Fig. 35 Fickian release fraction estimated for two cellulose-based hydrogels considering the polydatin liberation in a 5% ethanol aqueous solution

and discussed. Some experimental tools to get information concerning the formation process and structure of polymer networks and hydrogels were also discussed (e.g., light scattering, swelling analysis, FTIR, SEC, etc.). Having in mind the importance of the generation of materials incorporating cellulose, the synthesis of cellulose-based hydrogels, the modification of the physicochemical properties of cellulose through cross-linking, and the RAFT-mediated grafting of synthetic polymers in cellulose were also here described. It was shown that the morphology and the molecular architecture of polymer networks and hydrogels can be changed using tools such as the reactor type (e.g., operation in batch or continuous flow micro-reactor), the polymerization process (e.g., considering bulk, inverse suspension, or precipitation polymerization), and the polymerization mechanism, namely, FRP or RDRP (RAFT polymerization was mainly addressed here). Different case studies were presented to illustrate the practical use of the produced materials in diverse applications, namely, MIP hydrogel particles to target aminopyridines, MIPs for polyphenols, caffeine or 5-fluorouracil, and also cellulose cross-linked with epichlorohydrin for polyphenol retention. The use of cellulose-based hydrogels as controlled release vehicles for polyphenols was also here addressed, and results for the liberation of these kinds of molecules were presented, evidencing the non-Fickian mechanisms involved in such transport systems. The possibility for the use of supercritical CO_2 in the hydrogel impregnation process was also shown.

11 Future Developments

Results here presented show that many different tools can be used to address the tailoring of polymer networks and hydrogels. However, the most promising techniques are based on the use of RDRP mechanisms due to the improved precision achieved in the molecular architecture of such materials. Moreover, with RDRP mechanisms, namely, the RAFT-mediated process, it is possible to improve the control of the grafting of synthetic polymers on the cellulose backbone. Many different engineered products with complex structures can therefore be designed, namely, molecularly imprinted polymers incorporating natural polymers such as cellulose.

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Superabsorbent Aerogels from Cellulose Nanofibril Hydrogels

18

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Contents

Abstract

Deep eutectic solvents (DESs) are promising green chemicals that can function as solvents, reagents, and catalysts in many applications because of their biodegradability, ready availability, and low toxicity. Here, a DES of choline chloride–urea was used as a non-hydrolytic pretreatment medium to obtain cellulose nanofibril

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(CNF) hydrogels from recycled cellulose pulps (boxboard, milk containerboard, and fluting) and virgin birch cellulose pulp using a mechanical Masuko grinder. The mechanical disintegration of DES-pretreated cellulose fibers resulted in highly viscous, gel-like cellulose nanofibril hydrogels with shear thinning behavior. According to transmission electron microscope (TEM) imaging, the nanofibrils had widths from 2 to 80 nm, possessed the initial cellulose I crystalline structure, and had a crystallinity index of 53–56%. The nanofibril hydrogels obtained were further used to produce low-cost, ultralight, highly porous, hydrophobic, and reusable superabsorbing aerogels that were used as efficient sponges to absorb oil and chemicals. The nanofibril sponges prepared by the consequent hydrophobic modification (silylation) of CNF hydrogels and freeze-drying had ultralow density (0.003 g/cm^3) and high porosity (up to 99.8%). The sponges exhibited excellent oil/water absorption selectivity and ultrahigh oil (marine diesel oil, kerosene, gasoline, motor oil, castor oil, or linseed oil) and organic solvent (dimethyl sulfoxide, chloroform, n-hexane, toluene, acetone, or ethanol) absorption capacity. The nanofibril aerogels showed particular selectivity for marine diesel oil absorption from an oil–water mixture and possessed ultrahigh absorption capacities of up to 143 g/g, which were much higher than the commercial absorbent materials (i.e., polypropylenes) (9–27 g/g) used as references. Additionally, the absorbed oil could be recovered by means of simple mechanical squeezing, and the superabsorbent could be reused for at least 30 cycles.

Keywords
Aerogel · Cellulose nanofiber · Deep eutectic solvent · Nanocellulose hydrogel · Oil removal · Silylation · Sponge

1 Introduction

Cellulose nanofibrils (CNFs) are elemental constituents of plant fibers and possess unique mechanical and chemical properties, including superior strength and low density [1, 2]. Due to their very high water retention capacity [3] which is attributed to their hydrophilic surface hydroxyl groups, CNFs form highly viscous, shear thinning hydrogels with low solid contents. These hydrogels are attractive green alternatives to allow for the development of novel high-end applications. However, the individualization of intact nanofibrils and the production of their hydrogels are complicated and require intensive mechanical treatments because of the strong hydrogen-bonded structures of cellulose materials. Therefore, several different chemical and enzymatic pretreatments have been proposed to loosen the rigid structure of cellulose. Among the most promising new green chemicals to facilitate the production of CNFs and their hydrogels are deep eutectic solvents (DESs), which are readily available green compounds that have low toxicity and, in many cases, are biodegradable [4]. DESs are typically synthesized by complexation of a halide salt of quaternary ammonium or phosphonium cation as the hydrogen bond acceptor (HBA), along with a hydrogen bond donor (HBD) (e.g., urea, glycerol, or ethylene glycol), to form

a mixture that exhibits a notable lower melting point when compared to either HBA or HBD alone. The deep eutectic solvent system used in this research is based on choline chloride–urea as a pretreatment for the nanofibrillation of wood cellulose [5].

The CNF hydrogels can further be processed into various materials. Recently, the novel cellulose aerogels (also designated as cellulosic sponges or foam in the literature) based on CNF hydrogels have attracted considerable research interest due to their renewability, good mechanical properties, low density, high porosity, natural biodegradability, and environmental friendliness. These fascinating properties make it possible to use them as absorbents for oils and chemicals [6–12], for example. The aerogels can be prepared by freeze-drying the CNF hydrogel and removing all moisture while maintaining the porous, entangled 3D network structure of the CNFs. However, due to the presence of abundant hydroxyl groups, native cellulose aerogels display amphiphilicity (i.e., poor selectivity in absorbing hydrophobic compounds, such as oil, and high moisture absorption capacity) [13–15]. The hydrophobicity of the surfaces can be encouraged or created by introducing roughness (i.e., micro- or nanoscale asperities) and low surface energy substances. Typically, hydrophobicity is evaluated in terms of wettability by measuring the water contact angle (WCA) on material surfaces. Depending on their WCA value, materials are classified as hydrophilic, hydrophobic, or superhydrophobic. Materials with a WCA of less than 90° are described as hydrophilic; materials with WCAs of between 90° and 150° are hydrophobic; and those with WCAs of more than 150° are superhydrophobic [16].

High-capacity hydrophobic absorbents based on green materials are strongly desired for removing environmental pollutants, such as oil and chemicals spilled in the aqueous environment. For example, it has been estimated that 224,000 t of oil from oil tanker spills was released into the global marine environment between 2000 and 2011 [17]. In the explosion and sinking of the Deepwater Horizon oil rig in the Gulf of Mexico in 2010, the British Petroleum pipe had been leaking oil and gas on the ocean floor about 42 miles off the coast of Louisiana. By the time the well was capped 87 days later, an estimated 3.19 million barrels of oil had leaked into the Gulf, making the oil spill the largest accidental ocean spill in history. The potential magnitude of the environmental threat of oil pollutants can be gauged by the fact that 1 L of benzene can effectively render several million gallons of water unfit for human consumption [18]. Moreover, oil-contaminated water has a disastrous effect on aquatic and terrestrial life forms and also threatens human health and the economy – particularly tourism – due to its coating properties, unsightliness, and offensive odor [19]. Thus, there is an urgent demand across the world to develop a variety of technologies for the removal of oil and chemical pollutants from contaminated water sources.

Among the different cleanup methods available, such as in situ burning, mechanical methods, chemical treatments, and bioremediation alternatives, absorption through the use of oil and chemical sorbents is generally considered to be the optimal technological approach because of its relatively low cost, high efficiency, and production of less secondary pollution [17]. However, the feasibility of absorbents depends on their characteristics and performance. Hydrophobicity is one of their

most important properties as highly hydrophobic absorbents [20, 21] exhibit more efficient absorption of oil and many chemicals than low-hydrophobic absorbents. The cost of the absorbents must remain low due to the large volumes required for cleaning up such spills. Their environmental impact and costs are also affected by their ability to be reused and recycled. Overall, the capacity of absorbents is associated with their porosity and interaction with the contaminant (e.g., superhydrophobicity). Therefore, sustainable materials with superhydrophobic properties, good absorption selectivity, ability to float (buoyancy), recyclability, and cost efficiency are especially needed [22].

Conventional oil and chemical sorbent materials can be grouped into three major classes: inorganic mineral sorbents, synthetic polymer sorbents, and natural organic sorbents [23]. Inorganic mineral sorbents, also known as sinking sorbents, are highly dense, fine-grained mineral or inorganic materials (natural or processed) used to sink floating oil. Examples include fly ash [24], zeolites [25], exfoliated graphite [26], activated carbon [27], organoclay [28], silica nanoparticles [29], and silica aerogels [30]. Currently, these mineral sorbents are not widely used because of their low oil sorption capacities (typically less than 20 times by weight), poor oil/water selectivity, and low buoyancy, which make them difficult to recycle. Due to their inherent oleophilicity and hydrophobicity, synthetic polymer oil and chemical sorbents, including polypropylene fibers [31], polyurethane foams [32], and polypropylene nonwoven webs [33], are the commercial sorbents most commonly used to clean up spills. Despite their moderate oil sorption capacities, one major drawback of these sorbents is that they degrade or disintegrate very slowly, so their environmental and ecological effects are greater than those of mineral or natural products [34, 35]. In contrast, natural organic sorbents, including kapok [36], sugarcane bagasse [37], cotton [38], rice straw [39], and wood chips [40], are eco-friendly alternatives for removing oil and chemicals from wastewater. They have moderate oil sorption capacities (i.e., 3–50 times their own weight), which is comparable or sometimes lower density than inorganic and synthetic sorbents, and excellent biodegradability [41, 42]. Other advantages include their recyclability, their ability to recover oil and chemicals relatively easily, and the simplicity of their disposal when compared to other types of conventional sorbents. Despite these advantages, the majority of traditional natural sorbents also have many drawbacks, including poor buoyancy/floatability and poor selectivity of oil or chemical sorption, which is due to the relatively high water uptake of these inherently hydrophilic materials.

Here, the fabrication of CNF hydrogels based on a DES pretreatment and the use of hydrogels for the preparation of superabsorbent aerogels for the cleaning of oil and chemical spills is introduced. The CNF hydrogels were obtained from cost-effective recycled cellulose fibers (boxboard, milk containerboard, and fluting) using a simple, environmentally friendly nanofibrillation treatment involving a DES of choline chloride–urea. The CNF sponges were further synthesized from the hydrogels using a straightforward approach based on a reaction caused by a combination of two silylation agents followed by freeze-drying. The CNF aerogels had an ultra-low density (0.0029 g/cm^3) and high porosity (up to 99.81%) and were cost-effective, reusable, and hydrophobic. The increase in paper consumption has yielded a huge

amount of paper waste which contributes to 25–40% of global municipal solid waste [43]. Recycling paper waste will help to preserve forests as well as solve an environmental problem. Recycled cellulose fibers from paper waste are a cheap and abundant resource. Combining an aerogel structure with recycled cellulose fiber will form a new material that is cost-effective and promising in terms of its oil absorption. Prepared CNF sponges exhibited excellent oil/water selectivity and an ultrahigh capacity to absorb oil (marine diesel oil, kerosene, gasoline, motor oil, castor oil, and linseed oil) and organic solvents (dimethyl sulfoxide, chloroform, n-hexane, toluene, acetone, and ethanol). In addition, the absorbed oil was readily recovered by means of simple mechanical squeezing, and the superabsorbent aerogel could be reused for at least 30 cycles.

The chapter describes basic principle of manufacturing CNF hydrogels, which can be further processed into superabsorbent aerogels and how they can be utilized for the cleaning of oil and chemical spills. Utilization of renewable resources, low-cost raw materials, and simple and environmentally friendly manufacturing process makes these superabsorbents possible alternative for cleaning of chemical spills in the near future.

2 Materials and Methods

2.1 Chemicals

Urea (97%) and choline chloride (>98%) for DES were purchased from Borealis (Austria) and Algry Quimica (Spain), respectively. Methyltrimethoxysilane (98%, MTMS) was obtained from Evonik Industries (Germany), and hexadecyltrimethoxysilane (>85%, HDTMS) was purchased from Sigma-Aldrich (Germany). Lightweight marine diesel oil and kerosene were obtained from Neste (Finland), and gasoline (E95) and motor oil (5w40) were purchased from a local gas station. Dimethyl sulfoxide (>99%, DMSO) was obtained from TCI (Germany). Castor oil, linseed oil, chloroform (>99%), n-hexane (>98%), toluene (>99.9%), acetone (>99.8%), and ethanol (>99.9%) were obtained from VWR (Finland). All chemicals were used as received, without further purification. Two different types of commercial oil absorbent booms obtained from local rescue services were used as reference absorbents.

2.2 Raw Materials

Recycled boxboard and milk containerboard were collected directly from board-container collections, and fluting board was supplied by Heinola Fluting (Finland). A dry sheet of industrially bleached birch kraft pulp (*Betula verrucosa*) was used as a reference cellulose raw material. All pulps were first pulped without chemicals using a Kenwood KM020 pulper (UK), which has an operating principle similar to that of the Hobart pulper, at a consistency of 15% at approximately 45 °C using a rotor

speed of 2 for 10 min, and then washed and screened using a Somerville screen (Lorentzen & Wettre, Sweden).

2.2.1 DES Pretreatment and Preparation of CNF Hydrogels

To pretreat the cellulose pulps (boxboard, milk containerboard, fluting, and birch kraft), a DES solution was produced by heating 1620 g of choline chloride and 1223 g of urea in a large beaker (5 dm^3) at 100 °C until the mixture melted, after which it was placed into a water bath at 100 °C under constant stirring for approximately 5 min to obtain a clear, colorless liquid. Then, 25 g (abs) of cellulose material (moisture content of ~30%) was added to the suspension and mixed for 2 h, after which the beaker was removed from the water bath and 1000 cm^3 of deionized water was added while mixing [4]. Then, the treated cellulose was washed with water using a Somerville screen (Lorentzen & Wettre, Sweden) until clear rinse water was obtained.

Next, four batches of each pulp were treated with DES prior to nanofibrillation with a Masuko supermasscolloider grinder MKCA6-2J (Japan) (Fig. 1) to obtain cellulose nanofibril hydrogels. The stones of the grinder were first carefully brought into close contact, as observed by the low friction sound, and then the pretreated pulp slurry was poured into the grinder at a consistency of 1.5%. The pulp was passed through the grinder twice using a zero-grinding stone gap; then, the stones were adjusted to negative gap values to begin the actual nanofibrillation. The pulps were passed through the grinder a total of 10 times, using negative gap values of −20 μm, −40 μm, −50 μm, −70 μm, and −80 μm to obtain viscous CNF hydrogels.

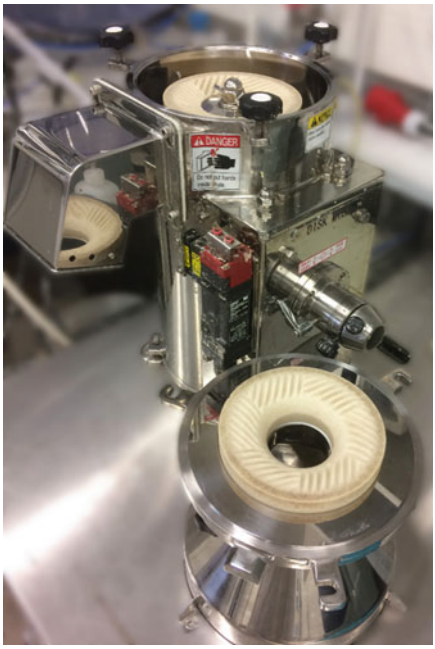

Fig. 1 Masuko supermasscolloider grinder MKCA6-2J and grinding stones

2.2.2 Visualization of Cellulose Nanofibrils

A Tecnai G2 Spirit transmission electron microscope (TEM) (the Netherlands) was used to observe the morphology of the CNFs. Samples were diluted with ultrapure water, and a small drop of the diluted nanofibril suspension was placed on a carbon-coated and polylysine-treated copper grid, and any excess sample was removed from the edge of the grid with filter paper. Negative staining of the samples was performed by placing a droplet of uranyl acetate (2% w/v) on top of each specimen. The excess uranyl acetate was removed with filter paper as described above. The grids were dried at room temperature and analyzed at 100 kV under standard conditions. Images were captured using a Quemesa CCD camera, and iTEM image analysis software (Olympus Soft Imaging Solutions GMBH, Germany) was used to measure the width of the individual cellulose nanofibrils.

2.2.3 Rotational Viscosity

Viscosity measurements of the CNF hydrogels were performed with the Brookfield DV-II+ Pro EXTRA (USA) rotational viscometer. For these measurements, vane-shaped spindles (V-71, V-72, and V-73) were used at rotational speeds of 10, 20, 50, and 100 rpm. The measurements were conducted at a sample consistency of 0.5% and at a constant temperature of 20 °C, using a measurement time of 2–5 min for each rotational speed.

2.2.4 X-Ray Diffractometry

The crystallinity of the cellulose nanofibril was analyzed through wide-angle X-ray diffractometry (WAXD) using a Siemens D5000 diffractometer (USA); Cu Kα radiation ($\lambda = 0.1542$ nm) was used for the measurements. As a pretreatment, the freeze-dried samples were pressed into tablets at a thickness of 1 mm, and the scans were taken over a 2θ (Bragg angle) range from 5° to 50° at a scanning speed of 0.02°/s, using a step time of 1 s. The degree of crystallinity, or the crystallinity index (CrI), was calculated using the peak intensity of the main crystalline plane (200) diffraction (I_{200}) of 2θ at 22.8° and a peak intensity of 2θ at 18.0°, which is associated with the amorphous fraction of cellulose (I_{am}), according to Eq. (1) [44].

$$\mathrm{CrI} = \left(\frac{I_{200} - I_{am}}{I_{200}}\right) \times 100\% \tag{1}$$

2.3 Fabrication of Hydrophobic CNF Sponges

The CNF hydrogels were diluted with deionized water, homogenized using an Ultra-Turrax system set to 8000 rpm for 30 s, and their pH adjusted to 4 using HCl. Various dilutions were used, depending on the sample (Table 1).

The silane solutions (20 wt%) for the hydrophobization of CNFs were prepared by diluting MTMS and HDTMS in ethanol. After dilution, hydrolyzed silane solutions were mixed using a magnetic stirrer for 10 min. Then, 25 wt% of freshly prepared

Table 1 Summary of CNF aerogel samples and references and solid content of CNF hydrogels used for aerogel preparation

Material	Abbreviation	Solid content of hydrogel (%)
DES birch cellulose	DES_Cel (1.0)	1.0
DES birch cellulose	DES_Cel (0.5)	0.5
DES birch cellulose	DES_Cel (0.3)	0.3
DES birch cellulose	DES_Cel (0.2)	0.2
DES fluting board	DES_Flu (0.5)	0.5
DES fluting board	DES_Flu (0.3)	0.3
DES fluting board	DES_Flu (0.2)	0.2
DES boxboard	DES_Boa (0.5)	0.5
DES boxboard	DES_Boa (0.3)	0.3
DES boxboard	DES_Boa (0.2)	0.2
DES milk containerboard	DES_MCB (0.5)	0.5
DES milk containerboard	DES_MCB (0.3)	0.3
DES milk containerboard	DES_MCB (0.2)	0.2
Ref boom polypropylene material (strip)	Ref (strip)	–
Ref boom polypropylene material (plug)	Ref (plug)	–

silane solutions (MTMS and HDTMS, ratio of 50:50) against CNF amounts were added by micropipette to the CNF suspensions and stirred with a magnetic stirrer at room temperature for 2 h.

Silylated CNF hydrogels (75 cm^3) were introduced into metallic, round molds (77 mm in diameter and 20 mm in height), frozen in liquid nitrogen, and transferred to the vacuum chamber of the freeze-drying device (Scanvac Coolsafe 55-15 Pro, Denmark) for 72 h to obtain hydrophobized CNF sponges. The silylation levels of the prepared sponges were determined by X-ray photoelectron spectroscopy (XPS).

The pH adjusting process is essential to promote the hydrolyzation of the silanes and to form the silanol groups that will later react with the cellulose nanofibers. Xie et al. [45] reported that cellulose is not reactive to many chemicals, and often the OH-groups are not accessible. Generally, the hydrolysis of organosilanes under acidic pH conditions favors the formation of more reactive silanol groups as well as the retardation of their condensation rate, which makes them available to react with the OH-groups of the fibers or to condensate over the fiber surface.

2.3.1 Density and Porosity of CNF Sponges and Reference Polypropylene Absorbents

The apparent volumetric mass density of CNF sponges and reference polypropylene materials was calculated using the following formula (Eq. 2):

$$\rho = \frac{m}{V} \tag{2}$$

where m and V are the mass (g) and volume (cm^3) of the materials, respectively.

Table 2 Density and porosity of CNF aerogels and commercial reference materials

Material	Density (g/cm^3)	Porosity (%)
DES_Cel (1.0)	0.0166	98.91
DES_Cel (0.5)	0.0070	99.54
DES_Cel (0.3)	0.0042	99.72
DES_Cel (0.2)	0.0029	99.81
DES_Flu (0.5)	0.0079	99.48
DES_Flu (0.3)	0.0049	99.68
DES_Flu (0.2)	0.0032	99.79
DES_Boa (0.5)	0.0075	99.51
DES_Boa (0.3)	0.0045	99.71
DES_Boa (0.2)	0.0031	99.79
DES_MCB (0.5)	0.0079	99.48
DES_MCB (0.3)	0.0048	99.69
DES_MCB (0.2)	0.0033	99.78
Ref (strip)	0.0807	91.11
Ref (plug)	0.0521	94.26

The porosity (P, %) of the CNF sponges and polypropylene materials was calculated according to Eq. (3):

$$P = \frac{V - m/\rho_c}{V} \times 100\% \tag{3}$$

where V (cm^3) is the volume of the materials, m (g) is the mass, and ρ_c is the density of bulk cellulose (1.528 g/cm^3) or polypropylene (0.9075 g/cm^3). Density and porosity of CNF sponges and commercial reference materials is presented in Table 2.

2.3.2 X-Ray Photoelectron Spectroscopy

The silylation levels of the prepared sponges were determined by XPS using a Thermo Fisher Scientific ESCALAB 250Xi (UK). A monochromatic Al$K\alpha$ X-ray source operated at 300 W was used with a combination of an electron flood gun and ion bombardment for charge compensation. The takeoff angle was 45° in relation to the sample surface. Low-resolution survey scans were taken using a 1-eV step and a 150-eV analyzer pass energy, and the high-resolution spectra were taken with a 0.1-eV step and a 20-eV analyzer pass energy. The binding energy (BE) scale was referenced to the C 1s line of aliphatic carbon, set at 284.6 eV. All measurements were taken in an ultrahigh vacuum pressure chamber (5×10^{-9} mbar).

Prior to measurement, a dry sample was pressed on the indium film. Three measurements were taken from each of the silane-treated CNF sponges. The first measurement was on top of the aerogel, the second at the bottom, and the third in the center of the aerogel after it had been sliced into two halves. The untreated reference aerogel was measured only once, the center.

2.3.3 Contact Angle Measurement

The surface wettability of the CNF sponges was evaluated using contact angle measurement. The static contact angles of Milli-Q water droplets on the aerogel surfaces were measured at 22 °C and 10% RH using a CAM 2000 (KSV Instruments Ltd., Helsinki, Finland). Measurements were performed by placing a 6.5-μL drop of Milli-Q water on the aerogel surface using a syringe and capturing images at a rate of 1 frame/sec to be sent directly from the CCD camera to the computer for analysis. Determination of the contact angle was based on an analysis of the drop's shape using the full Young-Laplace equation and assuming a spherical drop. The WCAs at 60 s are reported. Five parallel measurements were taken at various positions on each aerogel sample, and the average values and standard deviation were calculated. Typical uncertainties in the experiments were less than 5°.

2.3.4 Field Emission Electron Microscopy (FESEM) Characterization

To visualize the structure of the various CNF sponges, FESEM analysis was performed using a Zeiss Ultra Plus instrument (Zeiss, Germany). The samples were imaged using a low voltage (5 kV) and a working distance of ~5 mm. The CNF sponges were analyzed by simply placing each sample on a sample holder using a carbon pad and coating it with a thin layer of platinum.

2.4 CNF Sponges' Diesel Oil Sorption Selectivity from Oil–Water Mixtures

A fresh sorbent sample (0.05–0.1 g) was placed on the surface of a solution having a 5-mm layer (i.e., 13.00 g) of marine diesel oil floating on an 80-mm layer of water. The sample was left for 15 min, and then the sorbent was removed and left to drip for 30 s before being weighed. The amount of oil left in the oil–water mixture was determined using gravimetric analysis, as accepted by the United States Environmental Protection Agency (US EPA). In this case, diesel oil extracted using a solvent (i.e., n-hexane) from an oil-in-water sample is the EPA-accepted method (EPA 1664) for oil-in-water analysis. After sorption testing, the residual oil–water mixture was acidified to a pH of 2, and the sample was extracted three times using n-hexane. The combined collected extracts were distilled at 85 °C and weighed to determine absorption selectivity in terms of oil absorption capacity (g/g) and water uptake (g/g). At least three measurements were conducted for each sample, and the average value is presented.

2.5 Absorption Capacities for Various Oils and Organic Solvents

In the absorption test, pre-weighed hydrophobic CNF sponges were placed in various oils (marine diesel oil, kerosene, gasoline, motor oil, castor oil, and linseed oil) and organic solvents (dimethyl sulfoxide, chloroform, n-hexane, toluene, acetone, and ethanol) for 2 min to reach absorption equilibrium and then removed and weighed.

The sorption capacity (g/g), defined as the mass of absorbed oil or solvent (g) per unit mass of dry absorbent (g), was used to characterize oil absorption capacity. At least three measurements were conducted for each sample, and the average value is presented as an absorption result.

2.6 Reusability of CNF Sponges

Mechanical compression was used to extract the remaining liquid from the sorbent so that reusability could be tested. The absorbed marine diesel oil was recovered by simple mechanical squeezing. The squeezed CNF sponges absorbed oil again without any posttreatment, and the oil stored in the sponges was measured again. Oil storage capacity, defined as the mass of oil (g) per unit mass of the dry sponge (g), and values presented as capacity left compared to fresh absorbents were used to characterize the reusability of the CNF sponges.

3 Results and Discussion

A deep eutectic solvent based on choline chloride–urea was used as a pretreatment method to nanofibrillate recycled cellulose materials. Mechanical nanofibrillation (with a Masuko grinder) of the pretreated cellulose resulted in individual nanofibrils and an opaque CNF hydrogel. The method uses green bulk chemicals and can be considered a sustainable approach to obtain CNF without the need for toxic or expensive chemicals or other intensive mechanical and/or chemical modifications of the cellulose [46].

A few DESs are reported to dissolve cellulose [47], including a mixture of choline chloride and zinc chloride [48], and choline acetate with quaternary ammonium cation [49], when low-molecular mass microcrystalline cellulose is used. Here, subjecting oven-dried, high-molecular-weight cellulosic pulp to a DES mixture of choline chloride–urea with a molar ratio of 1:2 resulted in the disintegration of the cellulose into a solution without visible solubilization at 100 °C [4].

3.1 Appearance of CNF Hydrogels

During the DES treatment (before mechanical disintegration), the fibers rapidly formed a transparent, nonfibrous gel in the solvent, and after the addition of water, the fibers recovered their initial forms. Therefore, the DES-treated fibers did not show any clearly visible changes in their structures after being washed with water. When exposed to further mechanical disintegration, CNF hydrogels were obtained from the DES-treated fibers.

The visual appearances of these hydrogels after ten passes through the Masuko grinder are shown in Fig. 2. All of the CNF samples had gel-like, highly viscous appearances which indicate that the strong shear forces in the Masuko grinder break

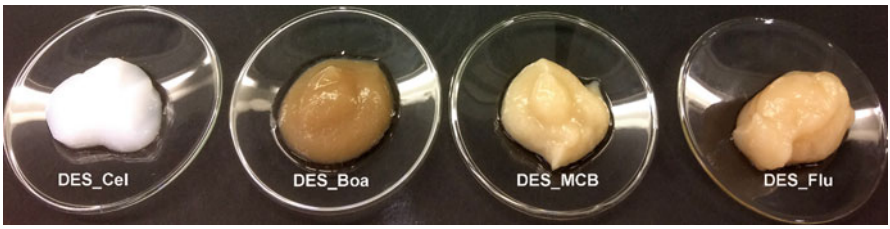

Fig. 2 Visual appearances of the CNF hydrogels (DES_Cel, DES_Boa, DES_MCB, and DES_Flu) after DES treatment and the 10th pass through the Masuko grinder. Solid contents of the hydrogels were between 1.5% and 2.0%

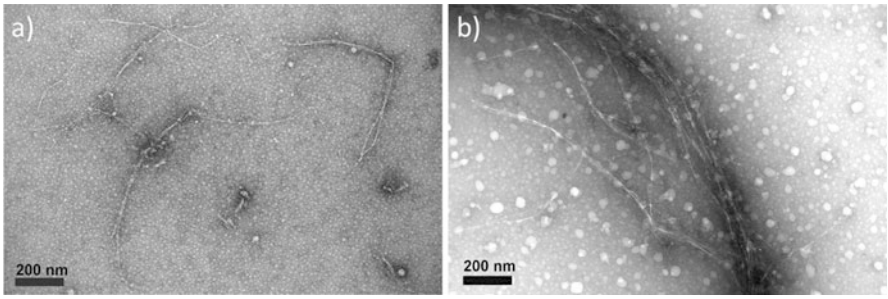

Fig. 3 TEM images of the DES_Flu (**a**) and DES_Boa (**b**). The white dots in the images are from the polylysine in the sample preparation

the hydrogen bonds in the loosened cell walls of the DES-treated cellulose fibers [2]. The choline chloride–urea was observed to promote the nanofibrillation of recycled fibers despite the high moisture content of the original cellulose material (approx. 70%). This result confirms the recent findings of Du et al. [50] who stated that a small amount of water absorbed into the choline chloride–urea solution can even improve the electrolyte system in the DES because water links to urea via strong hydrogen bonds, which in turn promotes ionic dissociation by the generation of more free cationic choline ions [50].

Figure 3 shows examples of TEM images of the CNFs after ten passes through the Masuko grinder. The visual appearances of the CNFs from different cellulose sources differed only slightly, and they all possessed diameters of 2–80 nm. Moreover, some larger aggregates were noted.

3.2 Rotational Viscosity of CNF Hydrogels

Figure 4 shows the rotational viscosities of the CNF hydrogels after their 10th (Fig. 4a) and the 8th passes (Fig. 4b) through the Masuko grinder at a consistency of 0.5%. The low shear rate viscosity of the hydrogel correlates with the morphology

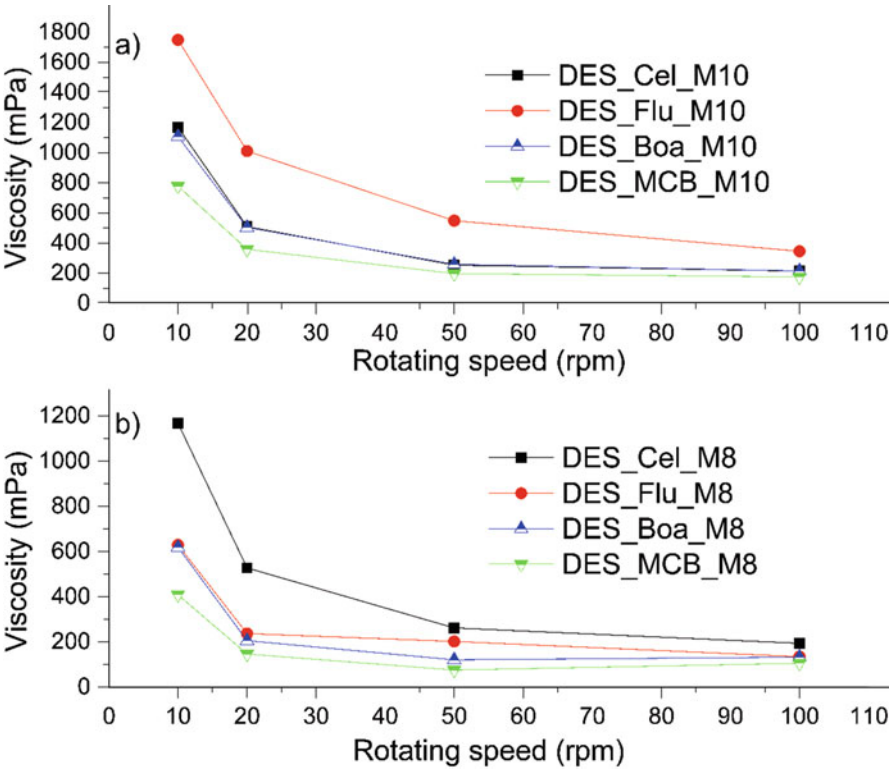

Fig. 4 Rotational viscosities of the CNF hydrogels (DES_Cel, DES_Flu, DES_Boa, and DES_MCB) and Masuko-ground pulps (**a**) after the 10th pass, and (**b**) after the 8th pass of the Masuko grinder at a consistency of 0.5%

of cellulose nanoparticles [51], and the higher the viscosity, the thinner and longer the nanofibrils are for a given concentration [52]. Long and thin nanofibrils are able to form network structures in aqueous phases held together by numerous temporary hydrogen bonds and van der Waals interactions [53]. This effect explains cellulose nanofibril hydrogels' thixotropic and shear thinning behavior that is related to the high aspect ratio of their particles [53, 54].

After eight passes through the Masuko grinder (Fig. 4b), the highest viscosity was observed for the CNF hydrogel obtained from virgin reference cellulose. However, all hydrogels showed high viscosity levels with shear thinning behavior after the 10th pass, thereby indicating that high-performing CNF hydrogels could be obtained from recycled fiber material. The use of recycled cellulose materials has a notable cost benefit, since the price of recycled cellulose materials is only around 10% of the price of bleached birch cellulose. In practice, the cost of recycled cellulose materials is only around 80–100 €/t, whereas the cost of bleached birch cellulose is currently around 700–800 €/t.

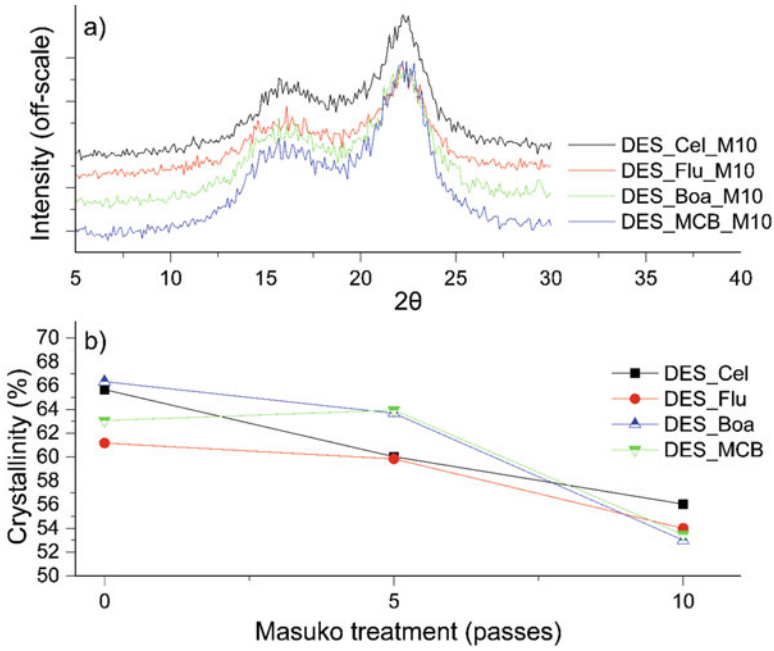

Fig. 5 (**a**) The diffractograms of the CNFs and (**b**) the calculated crystallinity indexes

3.3 X-Ray Diffractometry of the Nanofibrils

The X-ray diffractograms of the CNFs and the calculated crystallinity indexes are shown in Fig. 5a, b. The mechanical shearing caused a reduction in the crystallinity of the CNFs, and the largest reduction was noted after five Masuko grinder passes. The crystallinity index of the CNFs' tenth passes through the Masuko grinder varied from 56% to 53%, indicating that the CNFs still maintained their highly crystalline structure.

3.4 Hydrophobized CNF Sponges

The hydrophobized aerogels were produced from CNF hydrogels using consequent silylation and freeze-drying treatments. The waste cellulose materials (boxboard, milk containerboard, and fluting) were compared to virgin, bleached birch cellulose and found to be of sufficient quality and to present no problems during either chemical modification or fibrillation.

To achieve the porous structure of the CNF sponges (Table 2) and to avoid the need for posttreatment, both silylation agents – MTMS and HDTMS – were mixed with hydrogels before the freeze-drying process to result in cross-linked CNF aerogels while simultaneously improving their hydrophobicity. MTMS is a cross-linking

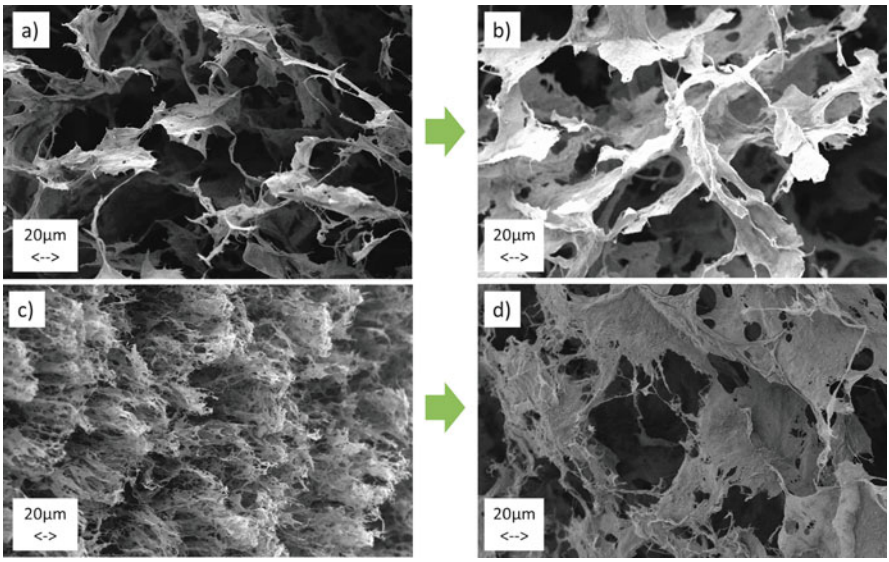

Fig. 6 FESEM images of CNF sponges: (**a**) unmodified DES_Boa (0.5), (**b**) modified DES_Boa (0.5), (**c**) unmodified DES_Cel (0.5), and (**d**) modified DES_Cel (0.5)

agent for cellulose [8, 55], while HDTMS is a silane containing a long carbon chain that can provide hydrophobicity in aerogels. The reaction medium was adjusted to an acidic pH of 4 to favor condensation of the hydrolyzed MTMS and HDTMS with the cellulose surface. At a pH of 4, the hydrolysis of alkoxysilanes has been reported as rapid and the self-condensation limited, which maximizes the concentration of the silanol species available to interact with the cellulosic substrate [56].

Table 2 shows the densities and porosities of the manufactured CNF sponges as a function of their CNF hydrogel solid content. Decreasing the solid content from 1.0% to 0.2% caused the density of the reference CNF sponge (DES_Cel) to decrease from 0.0166 to 0.0029 g/cm^3 and the porosity to increase from 98.91% to 99.81%. Compared to commercial oil absorption materials (i.e., polypropylene from commercial oil absorbent booms), the density of the CNF sponges was up to 28 times less and the porosity more than 8% more (Table 2).

Figure 6 shows the morphologies of the sponges made from recycled board and reference cellulose CNFs (DES_Boa and DES_Cel) with and without hydrophobic modification. Without silylation, the DES_Boa sponge possessed a continuous three-dimensional (3D) porous structure (Fig. 6a) that was formed by randomly entangled nanofibrils. Hydrophobic modification with the aid of a cross-linking agent resulted in the formation of a continuous, sheetlike coating. As demonstrated, the porous structure was well maintained (Fig. 6b, d). In addition, the waste board celluloses formed a well-structured texture when compared to the virgin cellulose aerogel (Fig. 6a–d).

Table 3 Water contact angles (WCAs) of various CNF aerogels with 0.5% solid content

Aerogel	WCA (deg)	WCA (std)
DES_Cel	142.9	6.65
DES_Flu	159.0	4.58
DES_Boa	107.2	4.45
DES_MCB	129.4	4.90

To indicate the hydrophobicity of silylated CNF sponges, their WCAs were determined (Table 3). All aerogels were evidently hydrophobic (i.e., WCA $> 90°$), and a sample of fluting celluloses (DES_Flu) could even be characterized as superhydrophobic (i.e., WCA $> 150°$). Based on visual observations, the water droplets easily rolled off the silylated CNF aerogels when the sliding angle was increased slightly, thereby confirming the hydrophobic nature of all silylated CNF sponges.

3.5 The Silylation Level of the Prepared CNF Sponges

Effective oil/water selectivity is essential for oil absorbents [9]. It should be noted that freeze-dried CNF sponges cannot be directly used as oil absorption materials due to the large number of hydrophilic hydroxyl groups in unsilylated cellulose fibers. Hydrophilic aerogels disintegrate rapidly in water because water penetrates the aerogel, destroying the hydrogen bonds between the CNFs and causing the aerogel structure to collapse.

The silylation of sponges was confirmed and quantified using X-ray photoelectron spectroscopy (XPS). Without silylation, the surface concentration of silicon in various DES-treated CNF sponges varied from 0.46 to 0.76 at.%, whereas after silylation, a strong peak of silicon was noted, and the surface concentration of silicon in these samples varied from 4.47 to 6.27 at.% (Table 4). In addition, the present study analyzed the spatial distribution of silicon on the top phase, the inner phase, and the bottom phase of the aerogel. The silicon contents were very similar (variation within 0.4%), except for that of DES_MCB (variation of 0.76%), which confirmed the successful, homogenous silane treatment of the aerogels (Table 4).

3.6 Diesel Oil Sorption Selectivity of CNF Sponges in Oil–Water Mixtures

To investigate the selectivity of oil sorption of various CNF sponges, a mixture of marine diesel oil and water was prepared. Figure 7 shows the oil absorption capacities of various DES-treated hydrophobic CNF sponges. All CNF sponges investigated demonstrated similar proclivities against porosity (i.e., solid content). With a solid content of 0.5%, all materials had nearly the same oil absorption capacity (from 88 to 97 g/g), while at higher porosities (i.e., $<0.5\%$), DES_Cel had the highest

Table 4 Silicon content of various CNF aerogels with 0.5% solid content

Aerogel	Surface concentration of Si on unmodified samples (at.%)[a]	Surface concentration of Si in silylated samples (at.%)[b]
DES_Cel	0.47	4.47 ± 0.27
DES_Flu	0.74	5.00 ± 0.34
DES_Boa	0.74	6.27 ± 0.36
DES_MCB	0.46	4.80 ± 0.76

[a]Silicon concentration (atomic weight) of aerogels prepared without silanes according to XPS analysis
[b]Silicon concentration (atomic weight) of silylated aerogels according to XPS analysis

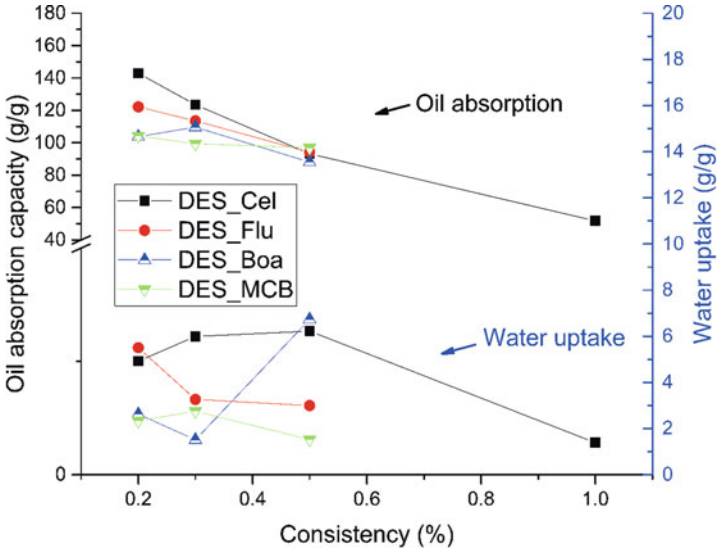

Fig. 7 Oil absorption capacities (left y-axis) and water uptake (right y-axis) of various CNF aerogels

capacity. Evidently, with increased DES_Cel sponge porosity (i.e., solids content from 1.0% to 0.2%), the absorption capacities for marine diesel oil increased significantly, from 52 to 143 g/g. Therefore, the CNF sponges with lower density and higher porosity possessed higher oil absorption capacities.

The water uptake, or water absorption, of various CNF aerogels was also determined, and the results are presented in Fig. 7 (right y-axis). In all cases, the water absorption of various CNF sponges was very low (<7 g/g) when compared to their marine diesel oil absorption (left y-axis of Fig. 7), suggesting that the various DES-treated hydrophobic CNF sponges had excellent selectivity toward diesel oil. Compared to the capacity of DES_Cel (0.3) to absorb water (6.0 g/g), DES_Cel capacity to absorb marine diesel oil could be as much as 21 times higher.

To achieve a very high absorption capacity (>100 g/g), CNF sponges should have the highest possible porosity and clear hydrophobicity. When porosity beyond 99.8% was achieved, problems were encountered because the strength of the CNF sponges was so diminished that handling them was a challenge. Another problem was that absorbed oil easily poured out from the aerogel structure after the oil sorption test, meaning that in practice the aerogel cannot retain all the oil that it absorbs.

3.7 CNF Sponges' Absorption Capacities for Various Oils and Solvents

The present study also investigated the capacity of hydrophobic CNF sponges to absorb a wide range of other oils and organic solvents, as shown in Fig. 8. Overall, the CNF sponges exhibited excellent oil absorption capacities. For example, DES_Cel (0.3) had a capacity of 124 g/g for marine diesel oil, 90 g/g for kerosene, 92 g/g for gasoline, 120 g/g for motor oil, and 150 g/g for linseed oil.

All CNF sponges also showed ultrahigh capacities to absorb a wide range of organic solvents, ranging from 65 g/g for hexane to 205 g/g for chloroform, depending on the density of the liquid (Fig. 8). These capacities could be attributed to the high porosity (99.72%) and hydrophobicity of the material. Comparing the results obtained for CNF sponges to those for commercial reference absorption materials (Ref (strip) and Ref (plug)), all the CNF sponges created had notably higher

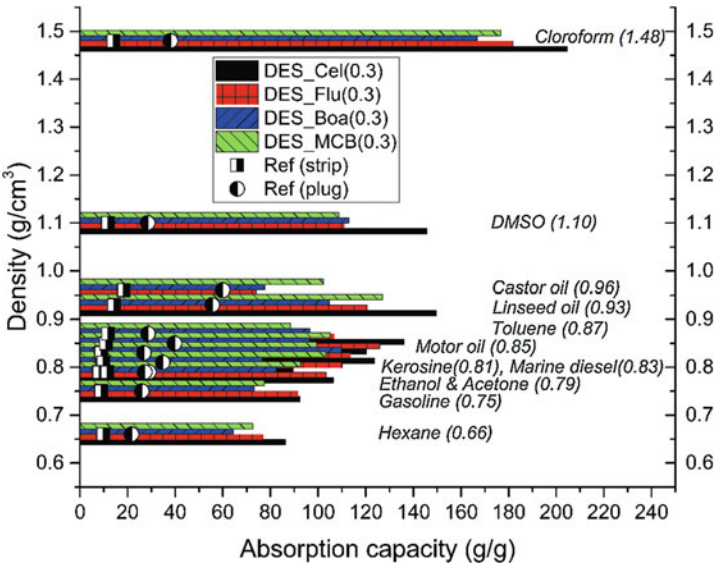

Fig. 8 Absorption capacities of various CNF aerogels and reference materials by the densities of oils and solvents

capacities to absorb all oils and organic solvents investigated. For instance, the DES_Cel (0.3) sponge had an absorption capacity of 120 g/g for motor oil and 136 g/g for toluene, while the DES_Boa (0.3) sponge had an absorption capacity of 96 g/g for motor oil and 97 g/g for toluene. In contrast, the Ref (strip) had an absorption capacity of only 11 g/g for motor oil and 12 g/g for toluene, and the Ref (plug) had values of 40 g/g and 29 g/g for these two liquids, respectively.

3.8 Reusability of CNF Sponges to Absorb Marine Diesel Oil

Figure 9 shows the absorption and reusability performances of the hydrophobic DES_MCB (0.5) sponge in absorbing marine diesel oil. Figure 9a shows how a water droplet stayed on the cleavage plane of the aerogel, thus indicating the CNF

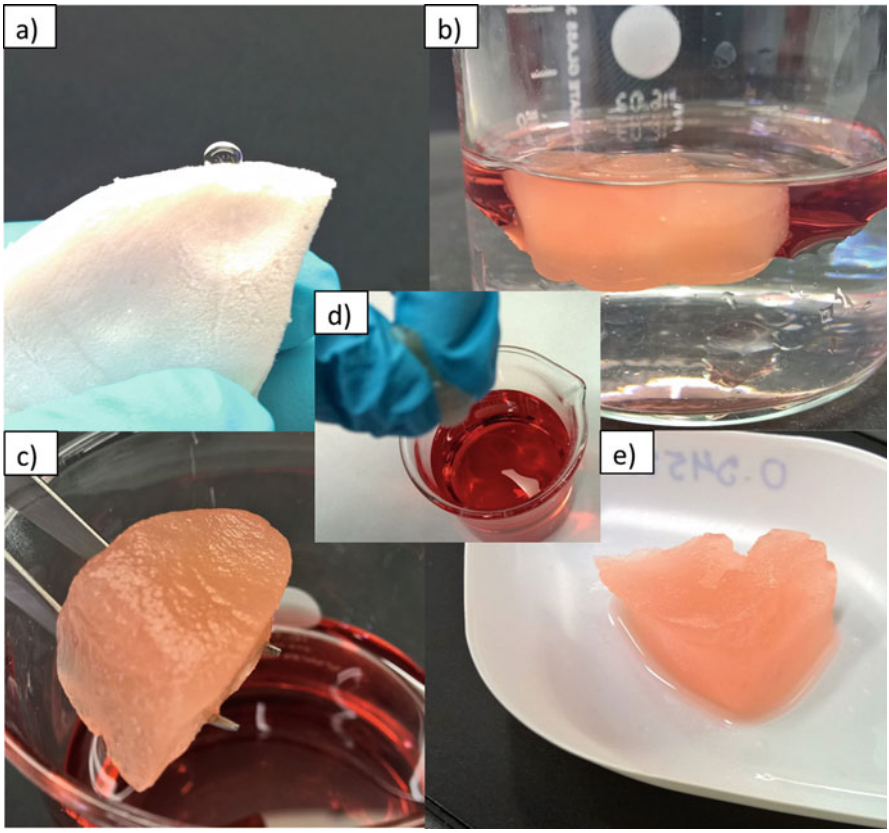

Fig. 9 High oil recovering efficiency and absorbent reusability of the hydrophobic DES_MCB (0.5) sponge. (**a**) Hydrophobic cellulose aerogel, (**b**–**c**) absorbing marine diesel oil, (**d**) squeezing absorbed oil, and (**e**) aerogel after 30 cycles of mechanical squeezing and reabsorption of marine diesel oil

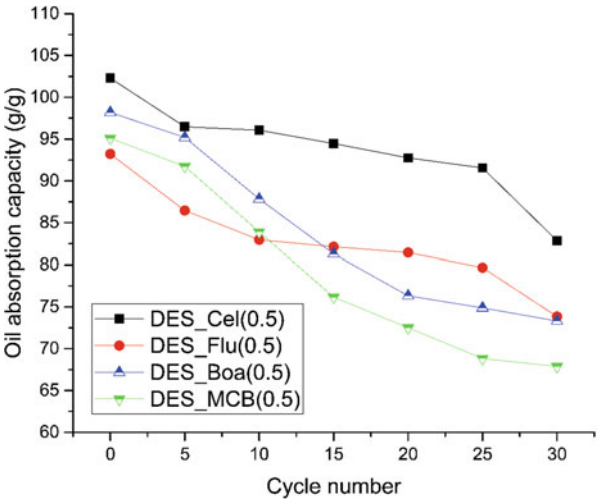

Fig. 10 Reusability of hydrophobic CNF sponges to absorb marine diesel oil

sponge's hydrophobicity. The sponge could be saturated with marine diesel oil in less than 30 s (Fig. 9b), thereby exhibiting its high absorption efficiency. In addition, the absorbed oil could easily be recovered by simple mechanical squeezing (Fig. 9c, d). Furthermore, the squeezed sponge could quickly reabsorb more oil over a period of about 30 s and recovered most of its volume without any posttreatment. Figure 9e demonstrates the appearance of DES_MCB (0.5) after 30 cycles of mechanical squeezing and reabsorption of diesel oil, demonstrating the sponge's efficiency in recovering oil and its reusability.

All DES CNF sponges could be reused, and the absorbed oil could be recovered by simple mechanical squeezing. Figure 10 shows the sponges' oil absorption capacities remaining after 30 squeezing-and-absorbing cycles. The oil absorption capacities of hydrophobic DES_Cel and DES_Flu sponges decreased by about 20 g/g, indicating their high reusability. Although the absorption capacities of the DES_Boa and DES_MCB sponges decreased to about 26 g/g, they retained more than two-thirds of their absorption capacities after 30 squeezing-and-absorption cycles. This performance has significant implications for various practical applications.

Compared with other methods of recovering or reusing absorbents, including distillation (heating) [57], rinsing (solvent extraction) [8, 58], combustion (burning) [59], and vacuum filtration [60], squeezing is probably the simplest and most sustainable in terms of its use of energy, materials, and chemicals. Many of the other methods of recovering oil and reusing absorbents, including distillation, solvent extraction, and burning, are complicated, time-consuming, inefficient, and energy intensive. Carbon fiber aerogels made from raw cotton [61] and waste pulp [62] have previously been mechanically squeezed to recover oil and then reused, but their

absorption capacity decreased dramatically in the second cycle, dropping to less than 55% of their original capacity. Therefore, mechanical squeezing could not be meaningfully applied to carbon absorbents in order to recover oil and reuse materials. Here, more than 70% of the absorbed diesel oil was efficiently recovered by facile, mechanical squeezing without the addition of other methods. Furthermore, the sponges could be reused for at least 30 cycles and maintained very high absorption capacities without sustaining significant structural damage. Oil absorbents with both ultrahigh absorption capacity and high efficiency in terms of their oil recovery and sorbent reusability are highly desired. Therefore, CNF sponges derived from waste cellulose using a green DES treatment prove to be promising for the cleaning of oil and chemical spills.

3.9 Comparison of Various Absorbents

Some of recently developed absorbents and their absorption capacities for various oils and organic solvents are listed in Table 5. Among them, carbon absorbents – either from carbon blocks, such as carbon nanotubes (CNTs) [63] and graphene [59, 64–66], or directly from carbonized materials, such as cotton fibers [61], cellulose fibers [62], and nanobacterial fibers [67], represent novel superabsorbents, demonstrating ultrahigh absorption capacities. Absorbents made from nanocellulose hydrogels exhibited low density and high absorption capacity for various oils and organic solvents (up to 200 g/g), arising from the good dispersion and stable suspension of CNF or CNC [8, 14, 68, 69]. The absorption capacity of nanocellulose fiber-based absorbents was slightly lower than that of carbon materials, but was considerably higher than that of other sorbents obtained from synthetic polymers (14–84 g/g) [70, 71].

In the present work, the marine diesel oil absorption capacity of the hydrophobic CNF aerogel prepared from CNF hydrogels was ultrahigh (88–143 g/g), and for chloroform it was up to 205 g/g, which was much higher than that of cellulose fiber-based absorbents, and was even comparable to that of most carbon absorbents (as listed in Table 5). Similar absorption capacities as found in the present research have been achieved using carbon nanotubes and graphenes [59, 64, 65], but the cost of carbon nanotubes could be as high as 100,000–600,000 €/t, and price of graphenes can be even higher. Furthermore, this research has demonstrated that absorbed marine diesel oil could be recovered in a fast and straightforward manner through simple mechanical squeezing and that the hydrophobic CNF sponge could be reused extensively without requiring any other posttreatment. The oil recovery method, absorbent recyclability, and costs were preferable to those of most of carbon-based absorbents. Therefore, as an ultralight, cost-effective, and highly recyclable superabsorbent, the hydrophobic CNF sponge has been demonstrated to be a possible alternative to carbon-based absorbents for the removal of spilled oil and organic pollutants from marine environments.

Table 5 Comparison of various superabsorbents developed recently

Year	Reference	Cost estimation	Absorbent	Oil recovery method	Absorption capacity (g/g)
2012	[63]	++	B-doped CNT sponge	Burning	25–125
2012	[64]	++	N-doped graphene framework	Burning	200–600
2012	[59]	++	Graphene sponge	Burning	60–160
2012	[65]	++	Spongy graphene	Distillation	20–86
2013	[66]	++	RGO foam	Burning	70–122
2013	[61]	+	Carbon fiber aerogel from raw cotton	Burning or distillation	50–192
2013	[62]	+	Carbon microbelt aerogel from pulp	Distillation	56–188
2013	[67]	++	Carbon nanofiber aerogels from BC	Burning	106–312
2014	[8]	+	Silylated nanocellulose sponge	Solvent extraction	49–102
2014	[14]	++	Silane-modified nanocellulose aerogel	Distillation	139–356
2014	[68]	++	PVA/cellulose nanofibril aerogel	–	44–96
2014	[57]	+	Carbon aerogel from winter melon	Distillation	16–50
2013	[70]	++	Poly(ODA-co-BA)	Solvent extraction	14–84
2014	[71]	+	PVF sponge	Squeezing	14–57
2013	[72]	–	Kapok fiber sponge	Squeezing	44–85
2014	[60]	–	Cotton	Vacuum filtration	20–50
2016	[12]	+	CNF aerogel	Evaporation	28–47
2017	[69]	+	Acetylated CNC	–	100–200
–	Present work	–	CNF aerogel	Squeezing	65–205

"–" low cost, "+" high cost, "++" very high cost

4 Conclusion

The chapter describes basic principle of manufacturing CNF hydrogels, which can be further processed into hydrophobic cellulose aerogels. Nanofibrillation, silylation, and freeze-drying are combined to create a porous, hydrophobic, superabsorbent CNF sponges. Utilization of renewable resources, low-cost raw materials, and simple and environmentally friendly manufacturing process makes these superabsorbents possible alternative for cleaning oil and chemical spills.

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Nanocomposite Hydrogels Obtained by Gamma Irradiation

19

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Contents

Abstract

During the past decades hydrogels have gained considerable interest and reviewed from different points of view, because of their unique properties. The hydrogel 3D structure, porosity, swelling behavior, stability, gel strength, as well as biodegradability, nontoxicity, and biocompatibility are properties which are widely variable and easily adjusted, making them suitable for many versatile applications, especially in the field of medicine and biotechnology. Generally, hydrogels possess the huge potential to be used as a matrix for incorporation of different types of nanoparticles. Namely, hydrogels in the swollen state provide free space between cross-linked polymer chains, in which the nucleation and

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growth of nanoparticles occurs. In this way, the carrier-hydrogel system acts as a nanoreactor that also immobilizes nanoparticles and provides easy handling with obtained hydrogel nanocomposites. It is well known that the properties of nanocomposite materials are dependent on the method of synthesis. Among various techniques, the radiation-induced synthesis offers a number of advantages over the conventional physical and chemical methods. Radiolytic method is a highly suitable way for formation of three-dimensional polymer network, i.e., hydrogels, as well as for generation of nanoparticles in a solution (especially metal nanoparticles). This method provides fast, easy, and clean synthesis of hydrogel nanocomposites. Moreover, and probably the most important from the biomedical point of view, is the possibility of simultaneous formation of nanocomposite hydrogel and its sterilization in one technological step. Despite all the mentioned advantages of radiolytic method, there are not so many investigations related to nanocomposite materials based on nanoparticles incorporated in a hydrogel matrix.

Keywords
Gamma irradiation · Hydrogels · Nanoparticles · Nanocomposites

1 Introduction

Nanotechnology is one of the fastest growing new areas in science and engineering. It is a cross-interdisciplinary area which involves the precise control and manipulation with atoms and molecules in order to create novel materials with unique unusual and/or enhanced properties. This technology requires detailed understanding of physical and chemical processes, across a range of disciplines, at the range below 100 nm. The main goal is production of new materials, devices, and systems tailored to meet the needs of a growing range of scientific and engineering applications. Moreover, the commercial application of such materials is probably one of the most important driving forces for so huge global activity in nanotechnology.

Polymer-based nanocomposites are being considered as versatile materials in many scientific applications leading to technological advancements. This is due to the fact that incorporation of the nanoparticles into polymer matrix significantly affects its optical, thermal, and electrical properties while retaining its inherent characteristics. It opens a new gateway in developing the materials for improved performance in many potential applications.

Polymers are considered to be a good host material for incorporation of inorganic nanoparticles. During the synthesis of nanoparticles, the atoms tend to coalesce into clusters, which grow into bigger particles or eventually into precipitates. The control of particle size can be achieved by the use of polymers such as capping agents. Functional groups of polymers ensure the anchoring of the molecule at the particle surface, while the polymeric chains protect particles from coalescing with other ones and thus inhibit at an early stage further coalescence through electrostatic repulsion or steric hindrance [1]. On the other hand, incorporation of nanoparticles, due

to their high surface to bulk ratio, can significantly affect the properties of the polymer matrix.

In the recent years, the novel and very attractive class of materials are the nanocomposites in which cross-linked polymer networks, i.e., hydrogels, are used as a carrier for the incorporation and organization of nanoparticles. The properties of such nanoscale devices can be tuned according to the required functions and applications. The "soft" mesoporous network of hydrogels is suitable matrix for incorporation of metal nanoparticles (Ag, Au) [2–5], magnetic particles (Fe_3O_4) [6, 7], as well as semiconductor nanoparticles (CdS, PbS) [8, 9]. Most of the technologies used to incorporate nanoparticles into polymeric matrix involve either chemical methods such as reduction, synthesis of complex compounds, mixing of preformed particles with polymers, or complicated physical techniques. Recent research efforts are directed toward exploiting possibilities for the *in situ* synthesis of nanoparticles within polymeric network architectures in order to produce enhanced and new hybrid nanomaterials. Three-dimensional network hydrogels are more suitable as templates for the production of nanoparticles than conventional nonaqueous or polymeric systems especially for biomedical applications, considering their exceptional compatibility with biological molecules, cells, and tissues. Hydrogels in the swollen state provide free spaces within the network, which can also serve for nucleation and growth of nanoparticles. In this way, the carrier-hydrogel system acts as a nanoreactor that also immobilizes nanoparticles and provides easy handling [10–14].

Beyond various techniques, the gamma irradiation-induced synthesis offers many advantages over the conventional physical and chemical methods. Radiolytic method is highly suitable for formation of three-dimensional polymer network, i.e., hydrogels, as well as for generation of nanoparticles in a solution (especially metal nanoparticles). This method provides fast, easy, and clean synthesis of hydrogel nanocomposites. Moreover, and probably the most important from the biomedical point of view, is the possibility of simultaneous formation of nanocomposite hydrogel and its sterilization in one technological step.

Despite all the mentioned advantages of radiolytic method, there are not so many investigations and literature related to nanocomposite materials based on nanoparticles incorporated in a hydrogel matrix. Therefore, some achievements in the field of radiolytic synthesis of nanocomposite hydrogels and their properties will be presented in this chapter.

2 Hydrogels

Hydrogels are two- or multicomponent systems consisting of a three-dimensional network of polymer and water that fills the space between macromolecular chains. Depending on the properties of the polymers used, as well as on the nature and density of the network joints, such structures in equilibrium can contain various amounts of water. Typically, in the swollen state, the mass fraction of water in the hydrogel is much higher than the mass of polymer. The hydrophilicity of the network

is due to the presence of chemical groups such as hydroxyl (–OH), carboxyl (–COOH), secondary amide (–CONH–), primary amide ($–CONH_2$), sulfonic ($–SO_3H$), and others that can be found within the polymer backbone or as lateral chains [15]. Nevertheless, it is also possible to produce hydrogels containing a significant portion of hydrophobic polymers, by blending or copolymerizing hydrophilic and hydrophobic polymers [16]. Hydrogels are one of the most promising materials for biomedical applications and have several advantages for wound dressing, contact lenses, drug delivery systems, etc. because of their biocompatibility with blood, body fluids, and tissue [17].

Two classes of hydrogel can be defined: physical gels or pseudogels and chemical or permanent hydrogels. In physically cross-linked gels, the macromolecular chains are connected by transient junctions that arise from either polymer chain entanglements or physical interactions such as ionic interactions and hydrogen bonds. Such types of gels are nonpermanent, and usually they can be converted to polymer solutions by heating. On the other hand, in chemically cross-linked hydrogels, covalent bonds are present between different polymer chains (permanent junctions). Therefore, they are stable and cannot be dissolved in any solvents unless the covalent cross-link points are cleaved [18, 19]. While physically cross-linked hydrogels have the general advantages of forming gels without the need for chemical modification or the addition of cross-linking entities, they also have limitations. It is difficult to decouple variables such as gelation time, network pore size, chemical functionalization, and degradation time; this restricts the design flexibility of a physically cross-linked hydrogel because its strength is directly related to the chemical properties of the gel constituents. In contrast, chemical cross-linking results in a network with a relatively high mechanical strength and, depending on the nature of the chemical bonds in the building blocks and the cross-links, relatively long degradation times. Chemically cross-linked gels are also mechanically stable owing to the covalent bond in these gels.

A special class of hydrogels, which is called stimuli-responsive or intelligent or smart hydrogels, shows an active and significant response (undergo reversible volume phase transitions or gel-sol phase transitions) to small changes in the surrounding environment [20]. Many physical and chemical stimuli have been applied to induce various responses of the smart hydrogel systems. The physical stimuli, which include temperature, solvent composition, light, pressure, sound, electric and magnetic fields, and mechanical stress, will affect and alter molecular interactions at critical onset points. Chemical stimuli, such as pH, ionic factors, and chemical agents, will change the interactions between polymer chains or between polymer chains and solvent at the molecular level. Recently, biochemical stimuli have been considered as another category that involves the responses to antigen, enzyme, ligand, and other biochemical agents. Some systems combine two stimuli-responsive mechanisms into one polymer system, the so-called dual-responsive polymer systems. Smart hydrogels have been used in diverse applications, such as drug delivery systems, in making actuators [21, 22] and valves [23, 24], in the immobilization of enzymes and cells [25, 26], in sensors [27, 28], and in concentrating dilute solutions in bioseparation [29].

3 Radiation Technology

In general, chemical or material engineering mostly applies high temperature and/or high-pressure processes for material synthesis/modification, and quite often a catalyst is required to speed up the reaction. On the other hand, radiation is the unique source of energy which can initiate chemical reactions at any temperature, including ambient, under any pressure, in any phase (gas, liquid, or solid), without use of catalysts [30].

Since the pioneering work of Wichterle and Lim in 1960 [31], the hydrogels have been of great interest, especially in the biomaterials field. In fact, hydrogels have been prepared by chemical methods for a long time. However, in recent years, irradiation techniques have been recognized as highly suitable tool to aid in the formation of hydrogels and being used increasingly around the world. This technology is convenient because the properties of hydrogels can be easily manipulated and adjusted by controlling the radiation dose and rate, and the process of synthesis is very reproducible [32]. The radiation process has various advantages, such as easy process control, the possibility of joining hydrogel formation and sterilization in one technological step (especially important for biomedical application), and the lack of necessity for initiators and cross-linkers, which are possibly harmful and difficult to remove. The radiation technique is clean, because it does not require any extra substances, does not leave some unwanted residues, and does not need any further purification. Moreover, this method has a relatively low running cost. All these qualities make irradiation the method of choice in the synthesis of hydrogels.

Hydrogels can be obtained by radiation technique in a few ways, including irradiation of solid polymer, monomer (in bulk or in solution), or aqueous solution of polymer. Irradiation of hydrophilic polymer in a dry form is rarely applied, so it will not be discussed here. More frequently used method is irradiation of monomer solution. This way is possibly most convenient when the chosen monomer is easily available but its polymer is not. In this method polymerization takes place in the first stage, followed by cross-linking of the formed chains. In this case, particular care has to be taken when using this method for the formation of hydrogels for biomedical use, because many of the monomers used are harmful or even toxic (contrary to the corresponding polymers). After irradiation of such systems, all unreacted residues have been fully extracted afterward, in a separate operation.

Among all methods, the most convenient method of radiation-induced synthesis of hydrogels is the irradiation of polymers in aqueous solution. Such systems, containing neither monomer nor cross-linking agent, are easier to control and to study. Also, with the application of this method, lower number of usually unwanted processes occurs, and hydrogels formed in this way are suitable for biomedical use with no need of further purification (synthesis and sterilization in one technological step) [33].

3.1 Synthesis of Hydrogels

When monomer or polymer solution is subjected to ionizing radiation, reactive intermediates are formed. This can result from direct action of radiation on the

monomer unit or polymer chains and from indirect effect, i.e., reaction of the intermediates generated in water with monomer or polymer molecules. Since the fraction of energy absorbed by each component of the monomer-water or polymer-water system is proportional to its electron fraction, which can be well approximated by the weight fraction, in dilute and moderately concentrated solutions, the indirect effect dominates [34].

It is well known that under the irradiation of aqueous solution, short-lived reactive intermediates of the water radiolysis, such as hydrated electrons (e_{aq}^-), hydroxyl radicals ($OH^\bullet$), and hydrogen atoms ($H^\bullet$), were formed first, and they react with the monomer units or polymer chains. Among these reactive species, hydroxyl radicals are the main species responsible for reactivity transfer from water to the monomer units or polymer chains. They abstract hydrogen atoms from monomer units or macromolecules, and thus monomer or polymer radicals are formed. In the case of monomer radicals, the processes of polymerization and cross-linking occur simultaneously, while the polymer radicals simply cross-linked to form polymer network [35, 36].

For the formation of hydrogels, the most important reaction of macroradicals is intermolecular cross-linking, i.e., recombination of radicals localized on two different macromolecules. Also, the other various reactions in systems can occur, and their importance and role in the competition with intermolecular cross-linking is not always fully recognized. These other reactions include reactions between two radicals, as intramolecular cross-linking as well as inter- and intramolecular disproportionation, and also processes involving one radical, as hydrogen transfer or chain scission. These processes do not result in joining the polymer chains; thus they do not lead to the formation of macroscopic gels [37].

However, during synthesis of hydrogels, an influence on the competition between inter- and intramolecular cross-linking always occurs (Fig. 1). At high polymer concentration (above the critical hydrodynamic concentration, which depends on the molecular weight), the probability that two recombining radicals are localized on different chains is relatively high. In such systems some physical entanglements may become permanent when the entangled chains become joined to the network in at least two points encompassing the entanglement site. The probability of intermolecular recombination decreases by the lowering of polymer concentration to a range where the macromolecules are separate (usually having a coil conformation). Besides concentration, another parameter of which is important for this competition is the way of irradiation, i.e., the dose rate. The combination of high dose rates (pulse irradiation with electron beam) with low polymer concentration may lead to the formation of several tens of even more than a hundred radicals located on every single chain. In these conditions the probability and yield of intermolecular recombination is greatly reduced [38].

Typical examples of simple polymers used for hydrogel formation by this method are poly(vinyl alcohol) (PVA) and poly(vinylpyrrolidone) (PVP). As already mentioned, the irradiation of an oxygen-free aqueous solution induces the radiolysis of water and generation of primary radicals (Eq. 1) [39]:

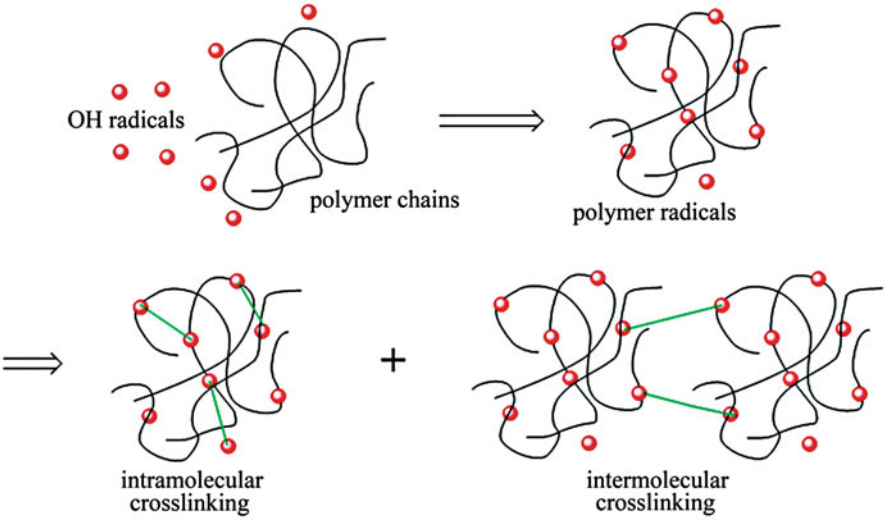
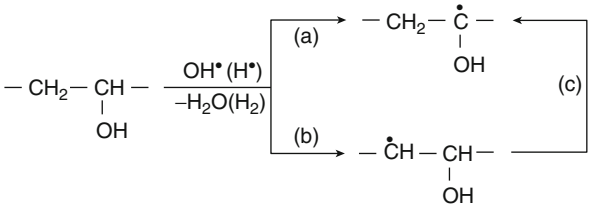


Fig. 1 Schematic representation of polymer cross-linking process (creation of intra- and intermolecular connections)

$$H_2O \rightsquigarrow e_{aq}^-, OH^\bullet,\ H^\bullet,\ H_3O^+,\ H_2,\ H_2O_2 \tag{1}$$

In the presence of PVA, both species ($OH^\bullet$ and $H^\bullet$ radicals) abstract preferentially a hydrogen atom in α-position to the hydroxyl group (–CH(OH)–) forming the tertiary radical (~70%) (Eq. 2a), but also from methylene group (–CH_2–) forming secondary radical (~30%) (Eq. 2b). The C-H bond dissociation energy of the secondary hydrogen is somewhat higher than that of the tertiary hydrogen, and therefore the process of radical activity transfer occurs (Eq. 2c) [40, 41].



(2)

These PVA radicals may interact with one another by recombination, disproportionation, and chain scission (by β-fragmentation) [42]. In the case of PVA, the degradation cannot be totally avoided, but its yield is low, and formation of polymer network occurs without any difficulty (G-value for intermolecular cross-linking is 0.48).

Similar situation occurs in the cross-linking process of PVP. The investigations of the reactivity of the primary products of radiolysis with polymer chains in the

process of hydrogel formations have indicated that the rate of reactions of solvated electrons is relatively low, with the rate constant in the range of 10^6 dm^3 mol^{-1} s^{-1}. Comparing this value with constant rate of reactions of hydroxyl radicals, which was determined as higher than 10^8 dm^3 mol^{-1} s^{-1}, it can be concluded that those radicals are the main species of water radiolysis which react with polymer chains [32, 38]. In argon-saturated aqueous solution, $OH^{\bullet}$ radicals attack PVP macromolecules by abstracting hydrogen atoms and thus producing macroradicals. It was suggested that the majority of macroradicals (about 70%) was localized on the main chain of a polymer and formed as a result of hydrogen abstraction at the methylidyne group. Moreover, hydrogen atom abstraction occurs also at methylene group adjacent to the nitrogen at pyrrolidone ring [43, 44]. The result of recombination of produced macroradicals is the formation of polymer network, i.e., hydrogel.

As already mentioned, irradiation can be used to synthesized the hydrogel from the monomer solutions. For example, hydrogels of poly(N-isopropylacrylamide/itaconic acid) (P(NiPAAm/IA)) can be synthesized by radiation-induced simultaneous polymerization and cross-linking of an aqueous solution of the monomers without any additional materials such as initiator and/or cross-linker [45]. In this case, monomeric radicals are generated by both the direct effect of radiation and the indirect effect based on the reaction of the products of water radiolysis with the monomers [35, 36]. In this way, first short-lived reactive intermediates of the water radiolysis, such as hydrated electrons (e_{aq}^-), hydroxyl radicals ($OH^{\bullet}$), and hydrogen atoms ($H^{\bullet}$), were formed and they react with the monomers. The double bonds of −C=C− on NiPAAm and of IA were broken, and generated free radicals react with each other and start copolymerization [46]. At low irradiation dose, the polymer network consists of chains united through multifunctional junctions with no or just few closed effective cross-links, thus forming giant molecules with branches and entanglements. But, by further irradiations, these reactive species can also abstract hydrogen from the growing polymer chains, producing thus polymer radicals that may further react and finally form cross-linked polymer network [36, 47, 48]. Radiation-induced copolymerization of NiPAAm and IA is a free radical process and can be represented by Fig. 2.

3.2 Synthesis of Nanoparticles Within Hydrogels

In general, the obtained polymer network possesses the huge hydrated space between cross-linked polymer chains and can be used as a matrix for formation of nanoparticles (NPs). In colloidal chemistry, the process of particle growth usually occurs through the Ostwald ripening mechanism. As a result, the particle size increases continuously during growth because the larger particles grow on account of dissolution of smaller ones [49]. A convenient procedure to restrict their growth is the *in situ* synthesis of nanoparticles within the polymer matrix with an improved architecture, i.e., within the three-dimensional network of hydrophilic polymers. Thus formed nanoparticles are entrapped in polymer network, and as a result, a novel inorganic/organic hybrid cross-linked nanocomposite was obtained.

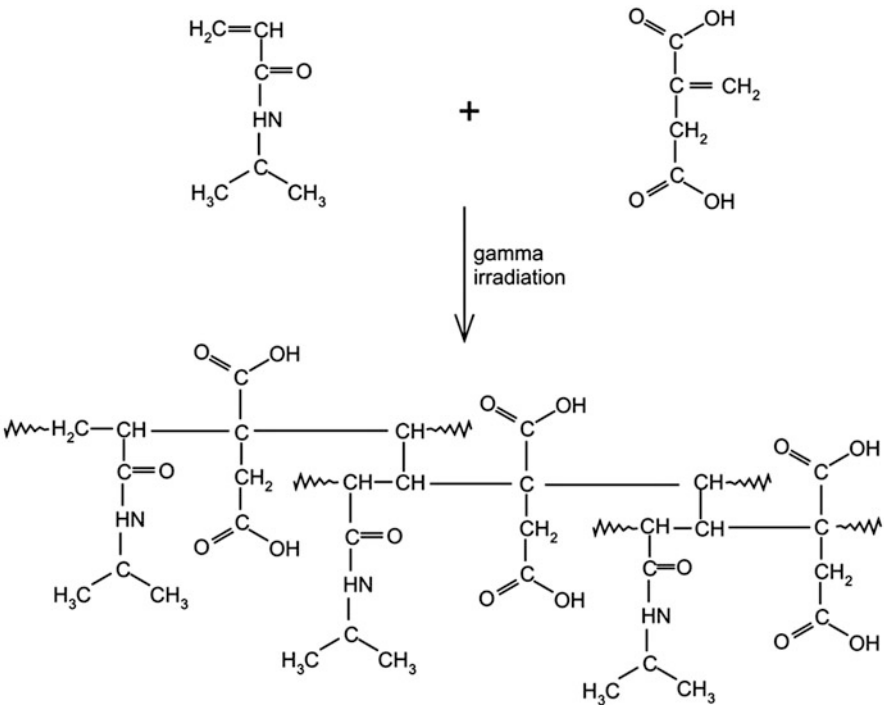


Fig. 2 Schematic representation of formation P(NiPAAm/IA) polymer network [45]

Synthesis of nanocomposites based on different types of nanoparticles incorporated into polymer network, i.e., hydrogels, can be conducted by several various pathways [50]. Not the easiest, from the practical point of view, but probably most convenient is the two-step synthesis procedure (Fig. 3) due to several advantages. The process of polymer cross-linking, as a separate step, in the absence of nanoparticles or their precursors (ions) allows formation of polymer network with the defined and stable 3D structure, further used as a template for incorporation of different types of nanofiller. On the other hand, in the second step of irradiation (synthesis of nanoparticles), this predefined structure of the polymer matrix and applied experimental conditions (absorbed dose and dose rate) can provide a control of size of nanoparticles and their homogeneous 3D distribution through the polymer network [51].

The preparation of metal nanoparticles has received increasing attention due to their unique properties. Noble metal particles such as silver and gold are of great significance due to their size-dependent optical properties [52–54]. Moreover, size effect was also observed for antibacterial activity of silver nanoparticles [55]. A large number of synthetic procedures have been employed in order to synthesize metal nanoparticles and/or nanocomposites. It has been shown that morphology, particle size distribution, stability, and properties of metal nanoparticles as well as corresponding nanocomposites are strongly dependent on the method of

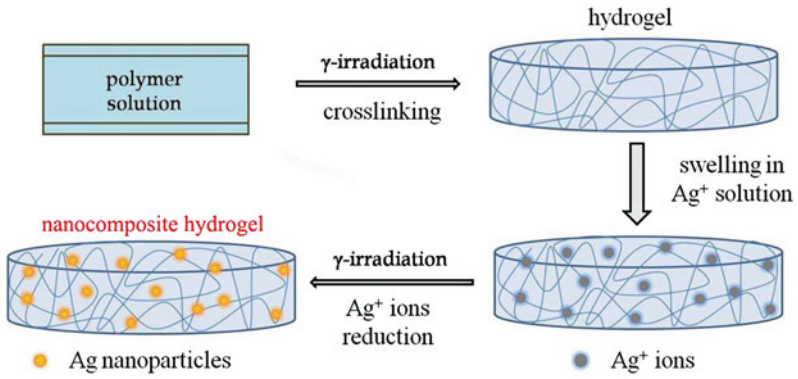


Fig. 3 The two-step irradiation-induced synthesis of nanocomposite hydrogels

preparation and specific experimental conditions. However, the synthesis of nanoparticles of desired shape and uniform size distribution within the matrix remains challenging.

The radiolytic method is suitable for generation of metal particles, particularly silver, in solution. The radiolytically generated species, solvated electrons and secondary radicals, exhibit strong reducing potentials, and consequently metal ions are reduced at each encounter, while the control of particle size is commonly achieved by the use of capping agents such as polymers [56–58].

The ions of noble metals, as well as of many electronegative metals, can be reduced by exposing their aqueous solutions to γ-irradiation. The main reactive radicals among the primary products are solvated electrons (e_{aq}^-), hydroxyl radicals ($OH^\bullet$), and hydrogen atoms ($H^\bullet$). The solvated electrons (e_{aq}^-) and hydrogen atoms ($H^\bullet$) are strong reducing agents, while the hydroxyl radicals ($OH^\bullet$) are able to oxidize the ions or the atoms into a higher oxidation state and thus to counterbalance the reduction reactions. For this reason, an $OH^\bullet$ radical scavenger is added in the solution. Among various possible molecules, the preferred choice is for solutes whose oxidation by $OH^\bullet$ yields radicals that are unable to oxidize the metal ions but, in contrast, themselves exhibit strong reducing power, such as the radicals of secondary alcohols. Most commonly used scavenger is 2-propanol which converts $OH^\bullet$ and $H^\bullet$ radicals into 2-propanol radicals ($(CH_3)_2C^\bullet OH$) (Eqs. 3 and 4) [57]:

$$(CH_3)_2CHOH + OH^\bullet \rightarrow (CH_3)_2C^\bullet OH + H_2O \quad (3)$$

$$(CH_3)_2CHOH + H^\bullet \rightarrow (CH_3)_2C^\bullet OH + H_2 \quad (4)$$

At the argon-saturated solutions, for example, Ag^+ ions are reduced into zero-valent Ag atoms (Ag^0) with strongly reducing hydrated electrons (Eq. 5), 2-propanol (Eq. 6), and the polymeric radicals (Eq. 7), formed in the hydrated polymer network structure as primary and secondary reactive species during gamma irradiation:

$$Ag^{+} + e_{aq}^{-} \rightarrow Ag^{0} \tag{5}$$

$$Ag^{+} + (CH_3)_2C^{\bullet}OH \rightarrow Ag^{0} + (CH_3)_2CO + H^{+} \tag{6}$$

$$Ag^{+} + \text{polymer}^{\bullet} \rightarrow Ag^{0} + \text{polymer} + H^{+} \tag{7}$$

The produced Ag^0 atoms are homogeneously dispersed throughout the hydrogel network. Because the binding energy between two metal atoms is stronger than the atom-solvent or atom-ligand bond energy, these Ag^0 atoms tend to dimerize (Eq. 8) when they encounter and/or associate with an excess of ions (Eq. 9) and by cascade of coalescence processes progressively grow (Eq. 10), yielding the formation of metal clusters with higher nuclearities:

$$Ag^{0} + Ag^{0} \rightarrow Ag_2 \tag{8}$$

$$Ag^{0} + Ag^{+} \rightarrow Ag_2^{+} \tag{9}$$

$$Ag_n + Ag^{+} \rightarrow Ag_{n+1}^{+} \tag{10}$$

The fast collision reactions of ions with atoms or clusters play very important role in the mechanism of cluster growth. Reduction processes of free and adsorbed Ag^+ ions (may be reduced at any stage of the coalescence) are competitive, and they are controlled by formation rate of reduction radicals. Therefore, the formation of clusters by direct reduction, accompanying with collision, is dominant at higher dose rate, when the nanoparticles with smaller dimensions were obtained [59, 60].

Furthermore, besides the metal nanoparticles, the irradiation method can be used for synthesis of semiconductor nanoparticles [9]. The mechanism of gamma irradiation-induced synthesis of semiconductor nanoparticles, in the presence of thiol, has already been known [61–63]. The thiol reacts with the solvated electrons (Eq. 11) and $OH^{\bullet}$ radicals (Eq. 12) to form hydrogen sulfide anion (HS^-) and thiyl radicals ($CH_3(CH_2)_{11}S^{\bullet}$), respectively:

$$CH_3(CH_2)_{11}SH + e_{aq}^{-} \rightarrow CH_3(CH_2)_{10}CH_2^{\bullet} + HS^{-} \tag{11}$$

$$CH_3(CH_2)_{11}SH + OH^{\bullet} \rightarrow CH_3(CH_2)_{11}S^{\bullet} + H_2O \tag{12}$$

When the gamma irradiation occurs in acidic solution (pH ≈ 5), thiol also can react with $H^{\bullet}$ atoms instead with solvated electrons (Eq. 11), but according to the rate constants, the reaction with solvated electrons is favored [63]. The thiyl radicals produced via reaction (12) dimerize to produce disulfide ($(CH_3(CH_2)_{11}S)_2$). Finally, the PbS molecules formed through reaction (13) and then coalesce to form nanoparticle (Eq. 14):

$$Pb^{2+} + HS^{-} \rightarrow PbS + H^{+} \tag{13}$$

$$n\text{PbS} \rightarrow (\text{PbS})_n \tag{14}$$

The final size of PbS nanoparticles can be controlled by concentration ratio of thiol/lead ions, as well as by the dose rate and total absorbed dose.

4 Nanocomposite Hydrogels

4.1 Nanocomposite Hydrogels with Silver Nanoparticles

Silver nanostructures, due to their size-dependent properties, exhibit significantly improved catalytic and electronic properties, and distinctive shape-dependent optical properties [52, 64], making them highly attractive for the use in the development of modern technologies. Morphological anisotropy of nanoparticles induces anisotropic optical absorption properties, bringing difference in the color, as well as optical absorption spectra, associated with the collective oscillations of the conduction electrons [65]. Silver, having the highest electrical and thermal conductivity among all metals, is an important material that has been used in various commercial applications [66, 67]. However, zero-charged nanocrystalline silver, i.e., silver nanoparticles (AgNPs), exhibits powerful antimicrobial capabilities and broad inhibitory biocidal spectra for variety of microbes, including bacteria, viruses, and eukaryotic microorganisms. Enhanced antibacterial properties of silver nanoparticles have been demonstrated both *in vitro* and *in vivo* [68–70].

From the practical point, nanocomposite systems with incorporated silver nanostructures are one of the most investigated new materials. Among all of them, special attention is paid to the nanocomposite hydrogels due to a wide range of applications. Hydrogels have the possibility to absorb large amounts of water and biological fluids; they are biocompatible, and therefore, they are often used in patient care and wound dressings [20]. Hydrogels facilitate autolysis and may be beneficial in the management of ulcers containing necrotic tissue. For example, debridement with hydrogels is more effective than standard wound care for healing diabetic foot ulcers [71]. A potential problem for the biomedical application of hydrogels is that microorganisms may grow in hydrogel materials because of their natural biocompatible properties. Therefore, the incorporation of antibacterial agents is required. However, the emergence of antibiotic-resistant bacteria as a result of the excessive use of antibiotics has led to a demand for newer antimicrobials. The increasing need to develop new formulations to solve this problem has led to considerable interest in the use of nanomaterials as new types of antimicrobials. It is well known that nanosilver has been proven to be probably the most effective antimicrobial agent. The multilevel antimicrobial mode of silver is particularly important for the treatment of wound infections in diabetic patients, which are usually polymicrobial, with the majority of infections being caused by aerobic Gram-positive *cocci* (predominantly *Staphylococcus aureus* and hemolytic *streptococci*) [72, 73].

The recent studies suggest that Ag nanoparticles exert toxicity to bacteria and other organisms not by direct particle-specific effect but by released Ag^+ ions [74]. When the pathways in the antibacterial activity and eukaryotic toxicity of Ag nanoparticles involve the Ag^+ ions and its soluble complexes, Ag nanoparticles

behave in analogy to a drug delivery system, in which the particle contains a concentrated inventory of an active species, the ions [75]. Although the importance of Ag^+ ions in the biological response to Ag nanoparticles is widely recognized, there is significant potential to improve nano-Ag technologies through hydrogel-controlled release formulations. Moreover, for the use of nano-Ag-loaded hydrogels in biomedicine, it should be possible to modulate the release of Ag^+ ions, which could be delivered to the patient at a controlled rate. This would allow the achievement of adequate concentrations and prolonged effectiveness. In general, it is known that the release of a soluble drug entrapped in a hydrogel should be closely related to the swelling characteristics of the hydrogels. That is because the release occurs only after the fluid penetrates into the polymeric network and dissolves the drug; this is followed by diffusion along the aqueous pathways to the surface of the device [76].

Krstić et al. [4] investigated the nano-Ag/PVA hydrogel device, synthesized by *in situ* gamma irradiation method, with the aim of designing a hydrogel-controlled release system of Ag^+ ions for antibacterial purposes. The *in vitro* Ag^+ ion release study showed sustained and controlled release in a solution with a pH similar to the biological fluids, with the release profiles of silver similar with the other drugs. Therefore, the elements of the drug delivery paradigm were applied for the study of Ag^+ ion release kinetics. It was found that the release of Ag^+ ions was predominantly controlled by a diffusion process, i.e., by the mass transport rate due to a concentration gradient of Ag^+ ions (Fickian diffusion). Moreover, the Ag^+ ion release can be adjusted by the concentration of AgNPs as well as by their size. The investigated nano-Ag/PVA nanocomposite hydrogels showed antimicrobial activity against Gram-positive *Staphylococcus aureus* and Gram-negative *Escherichia coli* [4].

Silver shows bactericidal activity at concentrations as low as 0.035 ppm without toxic effects to mammalian cells [77]. However, the typical minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) against standard reference cultures and multidrug-resistant organisms are 0.78–6.25 and 12.5 ppm, respectively [78]. A silver concentration of up to 1.2 ppm has no cytotoxic effect on fibroblasts *in vitro*, which play a critical role in wound healing. However, in general, cytotoxic effects seem to be dose-dependent [79]. The maximum toxic concentration for human cells is around 10 ppm. However, some authors have suggested that for topical use, Ag nanoparticles induce apoptosis at concentrations of up to 250 μg/mL (ppm), which could favor scarless wound healing [78]. Except for their use as antimicrobial topical dressings, nano-Ag/hydrogel systems could be applied for orthopedic implants, such as artificial cartilage, intervertebral discs, and artificial meniscus or tissue expander devices [80, 81].

When developing novel biomaterials, it is necessary to evaluate their biocompatibility and functionality, the latter of which is often related to certain biomechanical properties. Investigations of material functionality can be carried out by exposure of the material to *in vivo* conditions or to biomimetic simulations *in vitro*, followed by determination of the mechanical properties. *In vitro* conditions exhibit advantages in providing precise control and avoiding the complex *in vivo* environment. This type of investigation can be performed in biomimetic tissue engineering bioreactors. Bioreactor that mimics conditions in articular cartilage

and combines dynamic compression and medium flow through the cultivated tissue [82] was used to examine the mechanical behavior of Ag/PVP nanocomposite hydrogels [83]. Mechanical properties of investigated hydrogels varied from series to series, suggesting relative inhomogeneity of the PVP network and significant dependence of its properties to random processes of polymer cross-linking by radical polymerization and Ag^+ ion reduction. Having in mind high compression moduli of human articular cartilage [84], PVP and Ag/PVP nanocomposite hydrogels have not exhibited mechanical properties necessary for the use as soft tissue implants, but they meet requirements needed for the mechanical properties of wound dressings [83].

Biocompatibility of Ag/PVP nanocomposites was investigated by cytotoxicity assays in peripheral blood mononuclear cell (PBMC) and human cervix carcinoma cell (HeLa) cultures [79]. It was shown that the cytotoxicity of AgNPs released from Ag/PVP nanocomposites is dose-dependent, so that slight cytotoxicity is induced by Ag/PVP nanocomposites synthesized from 1 mmol dm^{-3} $AgNO_3$ solution. Kinetics of silver release was examined under static conditions, continuous SBF perfusion (in perfusion bioreactors), and under dynamic compression coupled with SBF perfusion (in the biomimetic bioreactor simulating *in vivo* conditions in articular cartilage). Diffusion was the dominant mechanism of silver release in static conditions and under SBF perfusion, while a slight contribution of dynamic compression was observed in the biomimetic bioreactor. Silver release kinetics modeling provided estimation of the time allowed for PBMC to be safely exposed to Ag/PVP nanocomposites under static and perfusion conditions (e.g., as wound dressings) of about 3 days. In wound dressing applications, it is a reasonable time for dressing replacement. In addition, it is estimated that concentrations of silver released from an Ag/PVP nanocomposite implant in articular cartilage in a knee joint would be well below the levels that would cause even slight cytotoxicity as determined in this study [79].

Among stimuli-responsive or intelligent hydrogels, from a biomedical point of view, thermo- and pH-sensitive polymers are the most frequently studied, because the temperature and pH are two factors that are most often changed in a physiological, biological, and chemical systems. Many previous works have been focused on the thermosensitive polymers because of their fundamental and technological interest [85, 86]. Poly(N-isopropylacrylamide) (PNiPAAm) is one of the most investigated thermosensitive polymers with a sharp lower critical solution temperature (LCST) between 30°C and 35°C for PNiPAAm (depending on the detailed microstructure of the macromolecules) [87]. The LCST represents the temperature at which the hydrophobic forces (due to interaction of the $-NCH(CH_3)_2$ groups), which lead to insolubility in an aqueous environment, are balanced by H-bonding with water, which maintains a polymer in solution. Below the LCST value, a hydration shell around the hydrophobic groups is formed by hydrogen bonds between the hydrophilic groups in the side chains and water, causing water uptake and swelling of the PNiPAAm. If the external temperature increases above the LCST, the scission of the hydrogen bonds occurs and hydrophobic interactions prevail, causing the leaching of water and collapsing of PNiPAAm, indicating the occurrence of phase separation and volume change. In general, it is well known that

the volume phase transition temperature (VPTT) of PNiPAAm-type hydrogel can be adjusted very near to human body temperature (between 37 °C and 41 °C, which is the temperature range of body in response to some diseases) by copolymerization or utilization of additives, which makes them suitable for *in vivo* applications. The addition of hydrophilic ionic comonomers, such as itaconic acid (IA), maleic acid (MA), or methacrylic acid (MAA), may provide that thermosensitivity of PNiPAAm can be controlled by pH value of the external media [88–91].

Spasojević et al. investigated dual-responsive, i.e., thermo- and pH-sensitive, Ag-P(NiPAAm/IA) nanocomposite hydrogel obtained by irradiation method [45]. It was shown that increasing of IA content in polymer network increases equilibrium swelling degree value of hydrogels, but it is also increases the VPTT. For the P(NiPAAm/IA) hydrogels, VPTT increases in the range from 30 °C to 42.8 °C with increasing of IA content in network from 0 up to 4.5 wt%. The same trend can be observed also for Ag-P(NiPAAm/IA) nanocomposite hydrogels, but with somewhat lower values of VPTT, in the range from 30.5 °C to 38.5 °C. Such results indicate that the fine-tuning of VPTT values can be achieved by incorporation of AgNPs in copolymer network.

The investigated homopolymeric hydrogels did not show pH dependence of the swelling degree, as expected. In contrast, the swelling of the copolymeric hydrogels was strongly dependent on the pH value of the external medium. At low pH values, the swelling degree was low because the carboxylic groups in the side chains were not ionized and intermolecular complexation via H-bonds occurred. This complexation results in increased hydrophobicity of the network and lower SD values [92]. As the degree of ionization increased above nominal pKa values of IA (pKa1 3.85 and pKa2 5.44) [93], the greater swelling degree was observed due to the three reasons: most of the H-bonds are broken, COO^- ions are more hydrophilic than COOH groups, and the electrostatic repulsion between the COO^- ions pushes the network chains apart. The most pronounced pH sensitivity was observed for the samples with highest IA content. Moreover, the incorporation of AgNPs induced slightly decrease in swelling capacity, in comparison with corresponding hydrogels without AgNPs. This was probably caused by the restriction of the large-scale segmental motion of the polymer chains and partial occupation of free space by AgNPs [4, 45]. Furthermore, by increasing of IA content, copolymeric hydrogels become weaker, and such mechanical behavior is in agreement with obtained network parameters. On the other hand, incorporation of AgNPs into polymer matrix improves mechanical properties, especially for systems with a higher IA content. As expected, investigated Ag-P(NiPAAm/IA) hydrogel nanocomposites showed good antibacterial potentials against both Gram-positive and Gram-negative bacteria [45].

4.2 Nanocomposite Hydrogels with Semiconductor Nanoparticles

Semiconductor nanoparticles or quantum dots, such as lead sulfide (PbS), cadmium sulfide (CdS), and zinc sulfide (ZnS), have specific optical and electronic properties

because of their quantum size and dielectric confinement effects. These properties are tunable by varying the size and the morphology of the particles. Nowadays, the challenge is to control these two factors in order to reach the best conditions, permitting the synthesis of adequate materials for advanced technologies.

Among semiconductor nanoparticles, PbS has been used in several areas such as light-emitting diodes, infrared detectors, optic fibers, infrared lasers, solar energy panels, window coatings, and environment as Pb^{2+} sensors [94, 95]. This wide range of applications is due to its interesting physical properties. The particularly narrow bandgap of PbS gives the possibility to tune the optical absorption in a large domain by reducing the size to the nanometric scale. But, the challenge is not only to synthesize extremely small PbS nanoparticles but also monodispersed ones. Several methods have been used to produce PbS nanoparticles in different environments such as zeolites, glasses, polymers, and inverse micelles or in colloidal state. The radiolytic method has been proven to be an adequate tool to synthesize monodispersed and size-controlled semiconductor nanoparticles. The particle size can be tailored by controlling the irradiation dose. In this way, PbS, CdS, and ZnS particles have been synthesized in the presence of mercaptoethanol [61–63].

Recent research describes a simple and effective method for preparation of PbS/PVA hydrogel nanocomposite [9]. Namely, the radiolytic *in situ* synthesis of PbS nanoparticles within the PVA hydrogel, previously cross-linked also by gamma irradiation, was achieved. The obtained PbS/PVA nanocomposite hydrogel shows the optical properties characteristic for semiconductor nanoparticles (quantization effects). The incorporated PbS nanoparticles are around 5 nm in diameter, with the bandgap energy of 1.84 eV. Incorporation of these nanoparticles into PVA hydrogel induces the slightly decreasing of swelling capacity of PbS/PVA nanocomposite hydrogel compared with PVA hydrogel. This probably occurs because the incorporated PbS nanoparticles can act as some sort of additional junction point in polymer network [96, 97]. Therefore, the thermal stability of PbS/PVA nanocomposite hydrogel is slightly enhanced.

This class of nanomaterials can be used for the fabrication of novel photonic materials and "solid-state" solar devices where the spacing between nanoparticles can be tuned for optimum photovoltaic efficiency. In particular, *in situ* growth of PbS nanoparticles in PVA 3D hydrogel matrix could produce soft 3D material nanocomposites with optical nonlinearity (metamaterials), opening perspectives for its application in special optical devices requiring small bandgap semiconductors embedded almost in water (optical properties of PVA are similar to water) [98, 99].

4.3 Nanocomposite Hydrogels with Magnetic Nanoparticles

The combination of magnetic nanoparticles with polymers in order to obtain colloidal or composite stable systems had attracted much interest. Magnetic nanoparticles are investigated in different areas because they are used in a wide range of applications in science, industry, and medicine. In particular, magnetic nanoparticles are used in data storage, medical drug delivery, hyperthermia, and bioseparation

[100]. Magnetic field sensitive gels (ferrogels) are new promising class of nanocomposite hydrogels. Zrinyi et al. developed magnetic field sensitive gels in which magnetic particles of colloidal size are dispersed and incorporated into the gels [101]. These ferrogels combine the magnetic properties of magnetic fillers and the elastic properties of gels. When the gels were placed into a spatially nonuniform magnetic field, forces act on the magnetic particles, and as result of strong interaction between magnetic particles and polymer chains, they all move together as a single unit. The coupling of hydrogels and magnetic particles has potential application in soft actuators such as artificial muscles [102]. On the other hand, recently the use of magnetic sensitive hydrogels has been explored for hyperthermia applications. The polymer networks have properties which make the hydrogels suitable for applications in controlled drug delivery systems, while the magnetic particles, with ferromagnetic or superparamagnetic properties, are used for magnetic hyperthermia [103].

In order to obtain magnetic sensitive hydrogels, magnetic nanoparticles can be incorporated in polymer network by loading coprecipitation technique as well as by radiation reduction technique [7]. In the both case, the hydrogel matrix was firstly obtained by irradiation-induced cross-linking of polymer chains. The synthesized quasi-spherical magnetite (Fe_3O_4) nanoparticles were well dispersed in the polymer matrix, with the average particle size around 30 nm. Investigated ferrogels possessed good loading capacity toward doxorubicin hydrochloride (model drug), while the releasing behavior was highly dependent on the pH values of the normal and tumor cells. The anticancer drug release was also affected by the difference between normal tissue that contains tightly connected endothelial cells which prevents the diffusion of the nanomedicines outside the blood vessel and tumor tissue which contains large fenestration between the endothelial cells allowing the nanomedicines to reach the matrix and the tumor cells [104]. These results may offer a suitable way for the preparation of anticancer drug carriers for tumor combination therapy aiming to increase anticancer activity and lower toxicity.

Moreover, ferrogels can be prepared by irradiation-induced cross-linking of polymer chains in the presence of magnetic nanoparticles [6]. In this case, the magnetite nanoparticles were synthesized by coprecipitation method, dispersed in the PVA solution, and exposed to the gamma irradiation to obtain nanocomposite hydrogel. This study shows that irradiation cross-linking of polymer in the presence of particles doesn't interrupt processes of intra- and/or intermolecular cross-linking of PVA chains, giving PVA/Fe_3O_4 ferrogel.

5 Conclusion

In general, nanocomposite hydrogels can be defined as cross-linked polymer network, swelled by water, with entrapped nanoparticles. The incorporated nanoparticles add unique physicochemical properties to polymer hydrogels such as responsiveness to mechanical, optical, thermal, sound, magnetic, electric stimulation, etc. These unique properties lead to applications in such different fields, such

as in the electronics, optics, sensors, actuators, and microfluidics sectors, as well as catalysis, separation devices, drug delivery systems, wound dressings, soft tissue implant, and many other biomedicine and biotechnological areas. The huge success of hydrogel systems as biomaterials lies in their resemblance to living tissue because of their high water content which minimizes the frictional irritation of surrounding tissue. Additional advantages of those materials are their nontoxicity, non-irritability, and chemical stability.

Nanocomposite hydrogels can be synthesized by different chemical and physical methods. Among them, irradiation-induced synthesis offers a number of advantages. This method provides fast synthesis and easiness of process control. Moreover, it is green and eco-friendly synthesis because there is no need to use the initiators, cross-linkers, and reducing agents; all reactions in the system are initiated by the product of water radiolysis. Probably the most important, from the biomedical point of view, is the possibility of simultaneous nanocomposite hydrogel synthesis and their sterilization in one technological step.

Despite all the mentioned advantages of irradiation-induced synthesis as well as the nanocomposite hydrogels prepared by this method, research in this area is not so much widespread.

6 Future Scope

In the field of nanocomposite hydrogels, as a relatively new class of hybrid materials, lies tremendous potential for future investigation and applications in many different fields. It is well known that using irradiation for synthesis and modification of nanocomposite hydrogels has numerous advantages, especially for production of biomaterials. On the other hand, it is still a long way to transfer research knowledge into production facilities, in order to extend the use of these materials. However, since the healthcare is one of the main priorities, it seems that research in this area will become even more important and the radiation technology will get an opportunity to show all possibilities.

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Effect of Irradiation for Producing the Conductive and Smart Hydrogels

20

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Contents

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Abstract

This review presents the past and current efforts with a brief description on the featured properties of conductive and smart hydrogel fabricated from biopolymers and natural ones for different applications. Many endeavors have been exerted during the past 10 years for developing new smart hydrogels. This review mainly focuses on the effect of different irradiation methods for improving the properties of smart hydrogels. As the hydrogels with single component have low mechanical strength, recent trends have offered composite or hybrid hydrogel membranes to achieve the best properties. So this chapter provides the reader good information about the irradiation effects on producing the smart conductive hydrogels and perspective on further potential developments.

Keywords

Hydrogel · Conductive · Smart · Irradiation · Cellulose

1 Introduction

Hydrogels are cross-linked polymeric networks that have the ability to swell when suspended in water. These absorbent polymers have a wide range of applications, such as sustained-release drug delivery systems, contact lenses, biosensors, personal care products, and medical, pharmaceutical, and agricultural fields. Hydrogels are macromolecular networks able to absorb and release water solutions in a reversible manner, in response to specific environmental stimuli. Such stimuli-sensitive behavior makes hydrogels appealing for the design of "smart" devices, applicable in a variety of technological fields. However, the functional hydrogel displays poor biocompatibility and biodegradability due to petrochemical products as the raw material. Therefore, using renewable resources as raw materials to prepare hydrogels is getting more and more attention. Temperature- and pH-sensitive hydrogels were prepared successfully by using natural polymers and their derivatives, such as chitosan, sodium alginate, dextran, cellulose, etc., as base materials. Cellulose and its derivatives have demonstrated to be versatile materials with unique chemical structure which provides a good platform for the construction of hydrogel networks with distinctive properties as respects swelling ability and sensibility to external stimuli. Indeed, the high density of free hydroxyl groups in the cellulose structure makes them become a solid substrate that can undergo functionalization, allowing the production of new materials for novel advanced applications. From the last decades, there is a growing demand for conductive devices with high performance due to the fast development of electronic industry. Lightweight, high conductivity, and flexibility as well as environmental friendliness are some requirements for these products. Considering the extensive possibilities to use the new materials, this chapter introduces the information on the intelligent conductive cellulose hydrogels, which are able to respond to environmental changes by modification of their characteristics, and finally presents their possible applications in different fields. From this reason, the

present chapter covers the applications of conductive cellulose-based hydrogels in different fields of industry such as the pharmaceutical and biomedical area. Moreover, a series of initiated techniques have been proposed for the production of cellulose-based hydrogels, such as chemical initiation, chemical cross-linking, UV-curing technique, and microwave, plasma, and gamma-ray irradiation. So this chapter provides the reader good information about the irradiation effects on producing the smart conductive hydrogels and perspective on further potential developments.

2 Hydrogels

Hydrogels are three-dimensional, hydrophilic, polymeric networks capable of absorbing large amounts of water or biological fluids. Due to their high water content, porosity, and soft consistency, they closely simulate natural living tissue, more so than any other class of synthetic biomaterials. Hydrogels may be chemically stable, or they may degrade and eventually disintegrate and dissolve. Hydrogels are called "reversible" or "physical" gels if molecular entanglements and/or secondary forces such as ionic, H-bonding, or hydrophobic forces play the main role in forming the network [1].

These absorbent polymers have a wide range of applications in biomedical area, such as sustained-release drug delivery systems; contact lenses; food; cosmetics; high water-absorbing resin; corneal implant; substitutes for the skin, tendons, ligaments, cartilage, and bone; biosensors; wound dressings; tissue engineering; and hygiene products (Fig. 1). Also, super porous hydrogels have been successfully used as soil improvers, slow-release fertilizers, and pesticide-release devices [2].

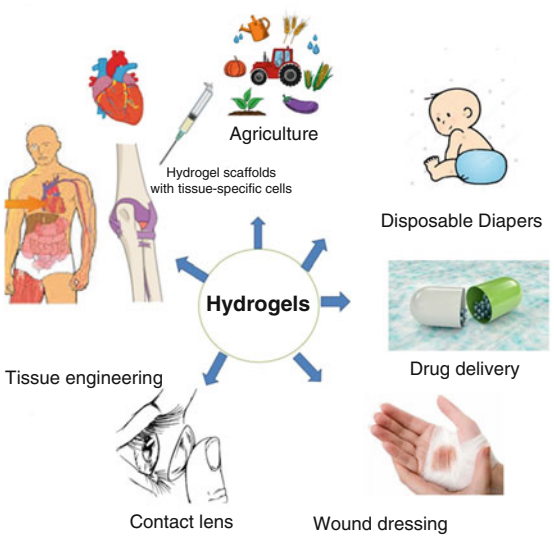

Fig. 1 Application of hydrogels in different branches of industry

The chemical cross-linking, physical entanglement, hydrogen bonds, and ionic bonds are responsible to achieve the network of hydrogels. They can be obtained from the synthetic and natural polymers and depend on various parameters, including the preparation method, charge, as well as mechanical and structural characteristics. It has been reported that the swelling of hydrogels is a complex process comprising of a number of steps. In the first step, the polar hydrophilic groups of the hydrogel matrix are hydrated by water, which appears in the form of primary bound water. In the second step, the water also interacts with the exposed hydrophobic groups, which appear in the form of secondary bound water. The primary bound water and the secondary bound water both form the total bound water. In the third step, the osmotic driving force of the network toward infinite dilution is resisted by the physical or chemical cross-links, so additional water is absorbed. The water absorbed into the equilibrium swelling is called the bulk water or the free water, which fills the spaces between the network or chains and the center of the larger pores. The amount of water absorbed by a hydrogel depends on the temperature and the specific interaction between the water molecules and the polymer chains, which can be explained by the Flory-Huggins theory [3].

It is worth noting that natural polymers have better biocompatibility and less latent toxic effect than most synthetic polymer hydrogels, so pure natural polymer hydrogels would be more suitable for biomaterials. Indeed, polysaccharide-based hydrogels behave as smart materials and offer a variety of properties that can be exploited in several applications. According to those abovementioned, cellulose represents the most abundant renewable and biodegradable polymeric material, being considered as the main constituent of plants and natural fibers. Also, cellulose is an environmentally friendly alternative to conventional materials and exhibits properties that make them very attractive in many applications. Nowadays, cellulose derivative-based hydrogel has gained a great popularity in agriculture and pharmaceutical industry and become more and more important in these fields, owing to the production of the new derivatives with extended applications [4, 5].

On the other hand, intelligent hydrogels, which exhibit sensitive responses to environment, such as temperature, pH, salt, electric field, and chemical environment, are widely applied in sensors, drug release, tissue engineering, and other fields. Various initiated techniques have been proposed for the preparation of smart hydrogels in the past few decades which include chemical initiation, UV-curing technique, microwave or gamma-ray irradiation, etc., but most of the chemical technologies had residual monomers and initiators and in some cases high energy consumption [6].

2.1 Cellulose Hydrogels

Most of the hydrogels are made from synthetic hydrophilic polymers such as poly (acrylic acid) or its copolymer with poly (acrylamide), but due to their biodegradability and low cost, the demand for using natural hydrogels such as starch, cellulose, chitosan, and alginate is continuously increasing. Cellulose is the

most abundant natural polymer and a very promising raw material with low cost for the preparation of its various derivatives [7].

Cellulose is the most abundant naturally occurring polymer of glucose, found as the main constituent of plants and natural fibers such as cotton and linen. Some bacteria (e.g., *Acetobacter xylinum*) are also able to synthesize cellulose. Microbial or bacterial cellulose (BC) is chemically identical to plant cellulose (PC), although possessing different macromolecular structures and physical properties. In both BC and PC, the glucose units are held together by 1,4-β-glucosidic linkages, which account for the high crystallinity of cellulose (usually in the range 40–60% for PC and above 60% for BC) and its insolubility in water and other common solvents. However, BC biosynthesis yields nano-sized fibers, which are about two orders of magnitude smaller than PC fibers. BC cellulose thus shows a peculiar, ultrafine fiber network with high water holding capacity and superior tensile strength compared to PC. Moreover, BC is totally pure, unlike PC which is usually associated with other biogenic compounds, such as lignin and pectin.

Most water-soluble cellulose derivatives are obtained via etherification of cellulose, which involves the reaction of the hydroxyl groups of cellulose with organic species, such as methyl and ethyl units.

The degree of substitution, defined as the average number of etherified hydroxyl groups in a glucose unit, can be controlled to a certain extent, in order to obtain cellulose derivatives with given solubility and viscosity in water solutions. Cellulose-based hydrogels, either reversible or stable, can be formed by properly cross-linking aqueous solutions of cellulose ethers, such as methylcellulose (MC), hydroxypropyl methylcellulose (HPMC), ethyl cellulose (EC), hydroxyethyl cellulose (HEC), and sodium carboxymethyl cellulose (NaCMC). Among the abovementioned cellulose ethers, only NaCMC is a polyelectrolyte and thus a "smart" cellulose derivative which shows sensitivity to pH and ionic strength variations [8–10].

2.2 Application of Cellulose Hydrogels

2.2.1 Superabsorbents for Personal Hygiene Products

A number of studies have been published in recent years documenting the advantages resulting from the use of superabsorbent materials in personal care products and their safety and effectiveness. In addition to keeping skin dry and preventing diaper rash, the SAP helps control the spread of germs in group care settings. The basic idea of diaper recycling is to recover separately the cellulose, which is biodegradable and recyclable, the plastic cover material, and the SAP, both of which are not biodegradable but might be recycled for other uses. The complexity of such a process has prompted the parallel development of biodegradable diapers, i.e., possessing a biodegradable plastic cover, which, however, still contain the nondegradable acrylate-based SAP. An alternative solution to the problem of SAP recycling has been recently suggested and has been envisaged in the use of cellulose-based hydrogels, which are totally biodegradable. Novel hydrogels, based on sodium carboxymethyl cellulose (NaCMC) and hydroxyethyl cellulose (HEC) cross-linked

with DVS, possess swelling capabilities comparable with those displayed by SAP and high water retention capacities under centrifugal loads. Cellulose radiation cross-linking, which does not require the use of further chemicals, might be of value in the development of novel environmentally friendly superabsorbents [5].

2.2.2 Water Reservoirs in Agriculture

There is an increasing interest in using superabsorbent hydrogels in agriculture. A few research studies have been carried out to determine appropriate hydrogel amounts and application rates for different environmental conditions and different plant species. It is worth noting that, being acrylate based, most commercial products are not biodegradable. Cellulose-based hydrogels fit perfectly in the current trend to develop environmentally friendly alternatives to acrylate-based superabsorbent hydrogels. Sannino and coworkers recently developed a novel class of totally biodegradable and biocompatible microporous cellulose-based superabsorbent hydrogels. Such hydrogels are able to absorb up to 1 l of water per gram of dry material, without releasing it under compression [5].

2.2.3 Body Water Retainers

Due to the intrinsic biocompatibility of cellulose, together with the biocompatibility and the versatile properties displayed by hydrogels in biomedical applications, cellulose-based hydrogels are appealing materials for a number of applications in vivo. For example, hydrogels hold promise as devices for the removal of excess water from the body, in the treatment of some pathological conditions, such as renal failure [5].

2.2.4 Devices for Controlled Drug Delivery

Cellulose ethers have long been used in the pharmaceutical industry as excipients in many drug device formulations. Their use in solid tablets allows a swelling-driven release of the drug as physiological fluids come into contact with the tablet itself. The cellulose ether on the tablet surface (e.g., HPMC) starts to swell, forming chain entanglements and a physical hydrogel. As swelling proceeds from the swollen surface to the glassy core of the tablet, the drug progressively dissolves in water and diffuses out from the polymer network. The rate of drug release depends on the water content of the swollen hydrogel, as well as on its network parameters, i.e., degree of cross-linking and mesh size. Controlled release through oral drug delivery is usually based on the strong pH variations encountered when transitioning from the stomach to the intestine [5].

2.2.5 Scaffolds for Regenerative Medicine

Due to their large water content, hydrogels are highly biocompatible, possess rubbery mechanical properties close to those of soft tissues, and usually allow the incorporation of cells and bioactive molecules during the gelling. In the last decade, the use of cellulose and its derivatives as biomaterials for the design of tissue engineering scaffolds has received increasing attention, due to the excellent biocompatibility of cellulose and its good mechanical properties. Nonetheless, it is well known that

a bio-durable material or a too slow degradation may lead to undesired biological responses (e.g., a foreign body reaction) in the long term, which limit the possible applications of cellulose in regenerative medicine. The mechanical stiffness of the hydrogel is also dependent on the degree of cross-linking and should be designed according to the tissues being addressed. Furthermore, the carbodiimide-mediated cross-linking reaction holds promise for the functionalization of cellulose with several biomolecules, able to promote specific cell functions, due to the ability of the carbodiimide to cross-link various polypeptides. This opens a wide range of possibilities for the design of biomimetic, cellulose-based hydrogel scaffolds for tissue engineering [5].

2.2.6 Wound Dressings

Appropriate wound dressings are designed to promote healing while protecting the wound from infection. Various types of hydrogel dressings have been patented so far and are commercially available, based on synthetic or natural polymers, or a combination of them. Due to its purity and high water retention capacity, bacterial cellulose (BC) has been widely investigated for wound healing, and a series of BC-based wound dressings are currently marketed. To the best of our knowledge, gel-forming cellulose derivatives, such as NaCMC, are included in the formulation of some commercially available hydrogel dressings, usually in combination with propylene glycol, which works as a humectant and a preservative [5].

3 Smart Hydrogels

Intelligent hydrogels, which exhibit sensitive responses to environment, such as temperature, pH, salt, electric field, and chemical environment, are widely applied in sensors, drug release, tissue engineering, and others.

3.1 Temperature- and pH-Sensitive Hydrogels

The most important kind of intelligent hydrogels has been paid special attention. Conventional preparations for temperature- and pH-sensitive hydrogels are radical polymerization, interpenetrating to introduce thermosensitive or pH-sensitive monomers, such as *N*-isopropyl acrylamide (NIPAAm) and acrylic acid (AA), and then the temperature- and pH-sensitive hydrogels with three-dimensional network are formed under the effect of cross-linking agents. However, the functional hydrogel displays poor biocompatibility and biodegradability due to petrochemical products as the raw material. Therefore, using renewable resources as raw materials to prepare hydrogels is getting more and more attention. Temperature- and pH-sensitive hydrogels were prepared successfully by using natural polymers and their derivatives, such as chitosan, sodium alginate, dextran, and cellulose as base materials, and all showed good performance. Moreover, hemicellulose, one of the three major components in plant biomass, exists in all cytoderm of plants (constituting about 20–30% of the

biomass). Statistical information shows hemicellulose is one of the most abundant and cheapest renewable resources. But as a result of the complexity and diversity of its structure, the application in intelligent hydrogels was rarely reported [5, 6].

3.1.1 pH-Responsive Hydrogels

Some researchers reported polymeric hydrogels with ionic pendant groups that can accept or donate protons in response to an environmental pH change. In a pH-responsive hydrogel at a specific pH, the degree of ionization known as pKa or pKb is dramatically changed. This rapid change in the net charge of the ionized pendant group causes a sudden volume transition by generating electrostatic repulsive forces between the ionized groups, which creates a large osmotic swelling force. There are two types of pH-responsive hydrogels: anionic and cationic hydrogels. Anionic hydrogels have pendent groups such as carboxylic or sulfonic acid, where deprotonation occurs when the environmental pH is above the pKa leading to the ionization of the pendent groups, which, in turn, increases the swelling of the hydrogel. On the other hand, cationic hydrogels contain pendent groups such as amine groups, where ionization takes place below the pKb, which increases swelling due to the increased electrostatic repulsions [5, 6].

3.1.2 Temperature-Responsive Hydrogels

Temperature-sensitive hydrogels are defined by their ability to swell and shrink when the temperature changes in the surrounding fluid, which means the swelling and deswelling behavior mostly depends on the surrounding temperature. Temperature-responsive hydrogels can be classified as positive or negative temperature-responsive systems [5, 6].

Positive Temperature Hydrogels

Positive temperature hydrogels are known by the upper critical solution temperature (UCST).

This means that when the temperature is below the UCST, the hydrogels contract and release solvents or fluids from the matrix (dehydration). At temperatures higher than the UCST, swelling takes place. In view of the above, it can be concluded that these types of hydrogels are retrogressive at negative temperatures. Positive temperature hydrogels shrink at low temperatures because of the formation of a complex structure by the hydrogen bonds. The structure dissociates at a high temperature due to the breaking of the hydrogen bonds, and the gel will swell to the maximum possible extent rapidly above the UCST. There are a lot of polymers and copolymers that are positively temperature dependent, such as poly (AAm-co-BMA) acrylic acid (AA) and *N*-isopropyl acrylamide (NIPAAm) as monomers and *N*,*N*-methylene double acrylamide (MBA) as cross-linking agents [5, 6].

Negative Temperature-PHGs

This kind of hydrogel has a critical parameter called low critical solution temperature (LCST), which means that the hydrogels will shrink when the temperature increases above the LCST and will show a swelling behavior when lower than the LCST.

The LCST is the most important parameter for negative temperature-sensitive hydrogels and can be changed in different ways, such as by mixing a small amount of ionic copolymer in the gels or by changing the solvent composition. In general, the LCST of a polymer with more hydrophobic constituent shifts to lower temperatures. By changing the ratio of hydrophobic to hydrophilic content of the structure of hydrogels, the LCST will be changed. Such hydrogels have two parts: the first is the hydrophilic part, CONH, and the second is hydrophobic part, R. At temperatures lower than the LCST, water or fluid interacts with the hydrophilic part by forming hydrogen bonds. Because of these hydrogen bonds, the dissolution and swelling will improve. As the temperature increases to greater than the LCST, the hydrophobic interaction with the hydrophobic part will be stronger, while at same time, the hydrogen bonds will become weaker. Therefore, shrinking of sample will occur due to the interpolymer chain association, and the absorbed fluid will go out through a deswelling process. An example is the PVP/PNIPAAm-based negatively thermosensitive drug release hydrogel [5, 6].

3.2 Stimuli-Responsive Hydrogels

Stimuli-responsive hydrogels respond to environmental stimuli and experience unexpected changes in their growth actions, network structure, mechanical strength, and permeability, hence called environmentally sensitive, smart hydrogels. Physical stimuli include light, pressure, temperature, electric fields, magnetic fields, mechanical stress, and the intensity of various energy sources, which change molecular interactions at critical onset points. Chemical stimuli include pH, ionic factors, and chemical agents, which change the interactions between polymer chains and solvents and between polymer chains at the molecular level.

Another class, which is called dual-responsive hydrogels, results from a combination of two stimuli-responsive mechanisms in one hydrogel system. Polyacrylic acid-co-polyvinyl sulfonic acid is an example of a dual-responsive polymer system. A biochemical stimulus involves the responses to ligand, enzyme, antigen, and other biochemical agents. So, stimuli-responsive hydrogels are attractive biomaterials for pharmaceutical, biomedical, and biotechnology applications [5, 6].

4 Conductive Hydrogels

Electroconductive hydrogels (ECHs) are polymeric blends or components that combine integrally conductive electroactive polymers (CEPs) with vastly hydrated hydrogels. Electroconductive hydrogels belong to the general class of multifunctional smart materials. As an emergent class, these materials seek to creatively combine the inherent properties of constituent materials, to give rise to technologically relevant properties for devices and systems as a bio-recognition membrane layer in various biosensors. In one instance, an electroconductive hydrogel that was synthesized from a poly(HEMA)-based hydrogel and poly(aniline) was fashioned

into a biosensor by the incorporation of the recombinant cytochrome P450-2D6. This electroconductive hydrogel was subsequently fully characterized for its electrical, switching, and optical properties and demonstrated faster switching than its purely CEP counterpart. In another instance, an electroconductive hydrogel fashioned from poly (hydroxyethyl methacrylate) [poly(HEMA)] and polypyrrole (PPy) was investigated for its potential application in the clinically important biomedical diagnostic biosensors, by the incorporation of analyte-specific enzymes. Among the various devices for which electroconductive hydrogel polymers were investigated are neural prosthetic and recording devices, electro-stimulated drug release devices, and implantable electrochemical biosensors. In all cases, these polymeric materials, which are both electronically and ionically conductive, provided a non-cytotoxic interface between the device and native living tissue or cell culture medium [3].

Conducting polymer hydrogels (CPHs) represent a unique class of materials that synergize the advantageous features of both the hydrogels and organic conductors. Conducting polymer hydrogels provide an excellent interface between the electronic-transporting (electrode) and the ionic-transporting phases (electrolyte), between natural and synthetic biological systems and between soft and hard materials. As a result, conducting polymeric hydrogels demonstrated promising results for a broad range of recent applications, ranging from energy storage devices, such as biofuel cells and super capacitors, to molecular and bioelectronics and medical electrodes. CPHs have been shown to provide excellent process ability and can be easily cast into thin films and any desired shapes at its gelation stage. CPHs can also be ink-jet printed or screen printed into micro-patterns. Hydrogels, based on conducting polymers, combine the several characteristics of polymeric hydrogels with the electrical and optical characteristic of metals or semiconductors, thus offering an array of features, such as intrinsic 3D microstructured conducting frameworks that promote the transport of charges, ions, and molecules [11].

5 Application of Smart and Conductive Hydrogels

Polyaniline (PANi), polypyrrole (PPy), and polythiophene (PTh) structures are some suitable raw materials. The synthetic routes toward conducting polymeric hydrogels include synthesizing a conducting polymer/monomer within a three-dimensional network of hydrogel. Through these methods, nonconductive hydrogels can be converted into conducting hydrogels via in situ polymerization technique of the electrically conductive polymers (ECPs) into the preformed hydrogel three-dimensional network.

Tang et al. developed poly(acrylateaniline)-based conducting hydrogels by employing in situ polymerization procedure [12, 13]. The first step includes the preparation of cross-linked polyacrylamide hydrogel in powder form, followed by in situ polymerization of absorbed aniline in the swollen hydrogel powder by employing potassium persulfate as an initiator. Furthermore, conducting polymer hydrogels (CPHs) have been prepared by various methods, such as the use

of electrically conductive polymer nanoparticles encapsulated into the three-dimensional hydrogel network. Recently, a few novel conducting hydrogels were developed based on only one material, such kind of materials (e.g., polyaniline (PANi), polypyrrole (PPy), polythiophene (PTh), etc.) as the continuous phase (conducting polymeric hydrogels).

Conducting polymer hydrogels (CPHs) have been applied as potential candidates in chemical mimicry of neural networks, implantable electrochemical biosensors, electro-stimulated drug release, etc. CPHs have been proposed as potential conductive flexible electrodes for super capacitor applications, and also it can be used for bioelectronics and energy storage devices and as glucose enzyme biosensors with high sensing speed and sensitivity applications. CPHs have promising applications in lithium-ion battery technology due to their excellent electronic and electrochemical properties. For instance, CPHs can be used to address the challenges faced by next-generation high-capacity alloy-based anodes, such as silicon and germanium. CPHs are a special class of polymeric hydrogels with potential advanced application in bioactive electrode coating, actuators, and tissue engineering field. Another important application has been found in biosensors, which integrate biological sensing elements, such as enzymes, antibodies, nucleic acids, cells, etc. with an electronic transducer equipped with an electronic amplifier.

CPHs possess a number of advantages, such as providing improved electrode interface between the electronic and ionic transport phases, a possibility of casting into different, complex, and flexible shapes and the possibility for the preparation of micro-patterns by ink-jet printing or spray coating [11].

To assist in identifying the utility of novel materials in drug delivery applications, one study investigated the use of bacterial cellulose (BC), a natural biopolymer, in the synthesis of hydrogels for drug delivery systems. The results of swelling and in vitro drug release studies revealed the hydrogels to be both thermo and pH responsive. Such thermo and pH responsiveness, in addition to their morphological characteristics, suggests that these BC/AA hydrogels are promising candidates as controlled drug delivery systems [14].

In the other research, graphene oxide reinforced regenerated cellulose/polyvinyl alcohol (GO–RCE/PVA) ternary hydrogels have been successfully prepared via a repeated freezing and thawing method in NaOH/urea aqueous solution. The effect of GO content on the mechanical properties, swelling behavior, and water content of composite hydrogels was investigated. With the addition of 1.0 wt% GO, the tensile strength was increased by 40.4% from 0.52 MPa to 0.73 MPa, accompanied by the increase of the elongation at break (from 103% to 238%). Meanwhile, GO–RCE/PVA ternary hydrogels performed the excellent pH sensitivity, and the higher pH leaded to higher swelling ratio. With 0.8 wt% GO loading, the swelling ratio of GO–RCE/PVA ternary hydrogel was improved from 150% (pH = 2) to 310% (pH = 14). In addition, a slight increase in the water content of the ternary hydrogel was achieved with increasing concentrations of GO. It is believed that this novel ternary hydrogel is a promising material in the application of biomedical engineering and intelligent devices [15].

In the other research, conductive hydrogel composed of microcrystalline cellulose (MCC) and polypyrrole (PPy) was prepared in ionic liquid; and hydrogels showed relatively high electrical conductivity, up to 7.83×10^{-3} S/cm [16].

Lignosulfonate (Lig), a biopolymer derivative, is a good candidate to be used as super capacitor electrode material because of its electroactive components. The methoxy and phenolic functional groups in Lig can convert to quinone groups through the redox process and function for energy storage. However, it is difficult to directly utilize Lig's electro activity, because of its insulativity. So a composite of Lig/graphene hydrogel (Lig-GH) has been fabricated from a mixture of Lig and graphene oxide (GO) via convenient hydrothermal process by Xiong et al. The results disclosed that the Lig-GH prepared at a mass ratio of Rm = 3:4 and temperature of 180 °C exhibited excellent electrochemical performance. The as-prepared hydrogel possessed high specific capacitance of 549.5 F g^{-1} at a current density of 1 A g^{-1} in 0.1 M $HClO_4$ electrolyte. It also showed excellent cycling stability: 83.7% capacitance retention after 1000 cycles at 20 A g^{-1}. This work provides an innovative strategy to prepare high-performance Lig-GH super capacitor electrodes material by introducing renewable and inexpensive biopolymers [17].

Chang et al. prepared superabsorbent hydrogels from carboxymethyl cellulose sodium (CMC) and cellulose in the NaOH/urea aqueous system by using epichlorohydrin (ECH) as cross-linker. The prepared hydrogels exhibited smart swelling and shrinking in NaCl or $CaCl_2$ aqueous solution, as well as the release behavior of bovine serum albumin (BSA) that could be controlled by changing CMC content [18].

New stimuli-responsive hydrogels have been invented based on inclusion of cellulose nano whiskers (CNW)-polyacrylamide (PAAm) copolymer in poly *N*-isopropyl acrylamide (PNIPAm) semi interpenetrating network (IPN) hydrogel. These hydrogels exhibit the highest equilibrium swelling ratio (ESR) in acidic medium (pH 4). Meanwhile they perform good swelling behavior and hydrophilicity at a temperature of 32 °C [19].

In the other research, electrically conductive hemicellulose hydrogels (ECHHs) have been successfully synthesized by a straightforward and robust approach by introducing the conductive aniline tetramer (AT) into hydrophilic, nontoxic, and biocompatible hemicellulose networks. By increasing the AT content, the SRs were tuned from 548% to 228% [20, 21].

In the other research work, a highly conductive nanocomposite was made with multiwalled carbon nanotubes (MWCNTs) and chitin nanofibers (ChNFs). It was found that the resultant ChNF/MWCNT gel-film exposed much more MWCNT areas forming denser structure due to the shrinking of ChNFs after the gelation treatment. Compared with ChNF/MWCNT film, the one treated under hydrogel system (ChNF/MWCNT gel-film) exhibited almost twice higher conductivity (9.3 S/cm for 50 wt% MWCNTs in gel-film, whereas 4.7 S/cm for 50 wt% MWCNTs in film) [22].

In many revolutions of the cellulose-based conductive materials, the most significant one was the developed material could be either directly used as a working electrode or used as the underlying substrate for the electrochemical deposition metal

electrodes. An in situ polymerization of aniline monomer onto the porous structured cellulose scaffolds has been carried out by Tian et al. and then electrodeposition of Ag nanoparticles on the obtained conductive composites directly by using it as electrode. The Ag nanoparticles were deposited homogeneously on the matrix of polyaniline (PANI)/cellulose gels. The conductivity of PANI/cellulose nanocomposite gels containing Ag nanoparticles was increased to 0.94 S C m^{-1}, which was higher than that of pure PANI/cellulose composites (3.45×10^{-2} S/Cm). Furthermore, it could be used as electrode for the super capacitors, and the highest specific capacitance of the cellulose/PANI/Ag aerogels was 217 F g^{-1}. This approach offered a facile method for improving the electronic conductivity of native polymer nano-hybrids and suggested a new strategy for fabricating nanostructured polymer nano-hybrids for application in energy storage [23].

The other research showed that the covalent incorporation of CNT into acrylate hydrogels composed of AAm and polyethylene glycol dimethacrylate (PEDGMA) as plasticizing monomer and cross-linker is a valuable strategy for the preparation of electroresponsive drug delivery systems suitable as topical devices (e.g., wound dressings) [24].

6 Irradiation Methods

The network of hydrogels, particularly those based on natural polymers, can be formed by different methods as chemical initiation or ionizing radiation from one component or two components by copolymerization, interpolymer complexes, and semi-interpenetrating polymerization. The irradiation methods are glow discharge, gamma-ray irradiation, electron beam irradiation, microwave, and ultrasonication. Aforementioned in the previous section, the pretreatment mechanism of each process is different according to the method applied. Physically cross-linked hydrogels usually show good biocompatibility but poor mechanical strength and stability. On the other hand, chemically cross-linked hydrogels usually exhibit enhanced mechanical strength and better stability but suffer from potentially harmful side reactions. Ionizing irradiation presents several advantages as it can occur without the need to add chemical initiators/cross-linking agent with subsequent separation of side reaction products. Moreover, the final products can be sterilized during hydrogel formation. Ionizing irradiation of polysaccharides leads to the chain scission and/or cross-linking reaction as a function of different parameters such as irradiation dose, irradiation phase, polymer concentration in aqueous solution phase, and the presence of oxygen. Usually, ionizing irradiation of polysaccharides at solid and non-concentrated solution states causes the breakage down of the chemical bonds between the repeated units of these polymers with consequent formation of lower-molecular-weight fragments. Moreover, the radiation dose can be easily controlled, and the experimental condition is simple for mass production of products. In addition, the product is free from undesirable chemical impurities such as residues from initiators, retarders, and/or accelerators for initiation and manipulation of the cross-linking reaction in chemical cross-linking methods.

6.1 Glow Discharge

The glow discharge owes its name to the fact that the plasma is luminous. This luminosity is produced because the electron energy and number density are high enough to generate visible light by recombination and excitation collisions. Glow discharges are used in a large number of applications. The light-emitting character of glow discharge has several applications such as in the light industry (the classical electrical discharge tube used in fluorescence lamps, neon discharge tube for advertisements, etc.), as the pump source for gas lasers, and as flat plasma display panels for the new generation of flat, large-area television screens. Besides, there are other important applications such as those in the microelectronic industry and in the material processing technology. These include surface treatment, etching of surfaces (for the fabrication of integrated circuits, etc.), plasma polymerization, plasma modification of polymers, and the deposition of thin protective coatings. Other forms of glow discharge for industrial applications are DC parallel plate plasma reactors, electron bombardment plasma sources, etc. In the simplest case, glow discharge is formed by applying a potential difference (of a few 100 V to a few kV) between two electrodes that are inserted in a cell or chamber filled with gas (an inert gas or a reactive gas) at a pressure ranging from a few mTorr to atmospheric pressure. Due to the potential difference, the electrons are accelerated away from the cathode and increase the collisions with the gas atoms and molecules. The collisions may produce processes such as excitation, ionization, dissociation, etc. The excitation collisions create excited species, which can decay to lower levels by the emission of light, and this is responsible for the characteristic name of the "glow" discharge. The ions are accelerated toward the cathode, and they release secondary electrons when bombarding at the cathode surface. These secondary electrons are accelerated away from the cathode, and they can give rise to more ionization collisions. Ionization collisions create ion-electron pairs, and this ion-electron multiplication process makes glow discharge a self-sustained plasma [25].

6.2 Gamma-Ray Irradiation

Gamma ray is a high-energy ionizing radiation in electromagnetic spectrum that easily penetrates most materials. This irradiation is extremely large high-frequency waves and largely depends on the radiation source. This technology is commonly applied in radiotherapy as a tracer in food and medical apparatus sterilization. Recently, the utilization of this technology has gain great attention especially in a biomass and biofiber pretreatment for liquid biofuel production. Radioactive nuclides such as cobalt-60 and cesium-137 are the common radioactive used in this pretreatment. The main goal of this irradiation is to decrease intra- and intermolecular order in cellulose due to the breakdown of the intermolecular hydrogen bonds. In this process, the radiation will travel from the seal source and penetrates (bombard) the biomass and biofiber. The energy carried by gamma radiation is transferred to the biomass component by collision of radiation, resulting to the loss of electron by

the atom and leading to the ionization. Under exposure to radiation, the biomass component mainly cellulose macromolecules undergoes scission, and various short- and long-lived radicals are formed. Also, the content of fragments with a low degree of polymerization generated from the process gradually increases, leading to the alteration of biomass structure, thus providing ease of access for subsequent process such as enzymatic saccharification process. The potential of gamma irradiation technology in biomass and biofiber pretreatment has been studied on various types of biomass, for instance, jute fiber, poplar sawdust, wheat straw, and cotton cellulose. There were only scanty studies on gamma irradiation pretreatment on tropical biomass and biofiber that have also been reported. A study on gamma irradiation of empty fruit bunches (EFB) indicated that the pretreatment has reduced the lignin and increased the cellulose content in the EFB. Scanning electron microscopy-EDX (SEMEDX) analysis showed that there is a significant change on the carbon and oxygen content in the EFB biomass. Typically, untreated EFB contains high carbon and low oxygen content, while the study found a decrease of carbon (9% increment) and decrease of oxygen content (16% decrease), indicating the reduction of lignin content in the EFB. A comparison of gamma-ray irradiation pretreatment on soft- and hardwood has also been carried out using different levels of dosage ranges between 10 and 100 kGy. The study found that the most suitable condition for softwood was at 40 kGy, while higher dosage is required to pretreat hardwood (90 kGy). The study also concluded that gamma-ray pretreatment process is species dependent, wherein higher dosage is needed to disrupt hardwood cell structure compared to softwood [26].

6.3 Electron Beam Irradiation

Electron beam is one of the irradiation pretreatments used to pretreat biomass prior to enzymatic saccharification. This technology has been widely used in various applications such as welding, drilling, and surface treatment. For commercial use, the most important characteristics of an accelerator are its electron energy and average beam power. Therefore, industrial electron accelerators are usually classified according to their energy ranges, which are divided into low (80–300 keV), medium (300 keV–5 MeV), and high energy ranges (above 5 MeV). In the electron beam pretreatment, the biomass and biofiber are exposed to a highly charged stream irradiation pretreatment of tropical biomass and biofiber for biofuel production electron. The electron is emitted from an electron beam gun and accelerated by accelerator. In this pretreatment process, the electron energy can be controlled and modulated by varying the irradiation dose. The high-energy electrons emitted travel into biomass and biofiber component and transfer the energy within the materials. The heating process initiates chemical and thermal reaction in the biomass including cellulose depolymerization and production of carbonyl group, resulting from the oxidation of the biomass. Cross-linking of biomass component has also been reported to occur when the biomass is exposed to irradiation beam. Also, reduction of the biomass mechanical strength has been observed from the biomass exposed to

electron beam. This could be due to the disruption of hydrogen bond between cellulose chains making it less crystalline and more amorphous [26].

6.4 Microwave Irradiation

Microwave is electromagnetic waves between the frequency range of 0.3–300 GHz, and most of the microwave systems used for industrial and domestic purposes range between 0.9 GHz and 2.45 GHz. Microwave radiation is a radiating wave movement and takes a straight-line path type of energy. This radiation does not require any medium to travel through and could penetrate nonmetal materials such as plastic and glass. Microwaves can affect the material thermally and nonthermally. Thermally, microwaves heat the material by the interaction of the molecules of material with electromagnetic field produced by microwave energy. Nonthermally, microwaves affect and interact with the polar molecules and ions in the materials causing physical, chemical, and biological reactions [26].

6.5 Ultrasonication

Another irradiation pretreatment that is widely used to pretreat biomass and biofiber for biofuel production is ultrasonication. This process can be performed either using probe-type ultrasonication or an ultrasonic bath. In this process, ultrasonic waves can be generated via piezoelectric or magnetostrictive transducers in the frequency range of 20–1000 kHz, in which the waves induced provide pressure difference in the medium. The pressure wave that travels through the liquid medium has high-pressure (compression) and low-pressure (rarefaction) regions. The rarefaction of the cycle can stretch the liquid molecules apart and create cavities also known as bubbles. As the wave cycles through the liquid, the bubbles expand and contract with the rarefaction and compression of the wave, respectively, drawing more liquid molecules into the bubbles as they grow. The bubbles that either continue to expand and then float to the surface are subjected to coalescence due to the forces or collapse during compression of the wave. This collapse is almost adiabatic and can result in localized temperatures of around 5000 K and pressures of 1000 atm. The collapse results in the formation of radicals through dissociation of the molecules within and around the bubbles, luminescence due to excited molecules formed losing energy, and micro jets shooting out of the bubbles of speeds in the realms of hundreds of km per hour [26].

7 Glow Discharge Effects on Hydrogels

Various initiated techniques have been proposed for the preparation of hydrogels in the past few decades which include chemical initiation, UV-curing technique, microwave or gamma-ray irradiation, etc., but all these trigger technologies had residual

monomers and initiators, high energy consumption, etc. Glow discharge electrolysis plasma (GDEP), which belongs to the nonequilibrium plasma, exhibits the characteristics of non-faraday because it produces numerous highly active particles in plasma electrolysis, such as $HO^{\bullet}$, $H^{\bullet}$, $HO_2^{\bullet}$, e_{aq}^{-}, and H_2O_2.

In addition, GDEP was used in organic synthesis, wastewater degradation, surface modification, and other fields due to its simple equipment, low energy consumption, and no environmental pollution [6]. The temperature/pH dual sensitivity reed hemicellulose-based hydrogels have been prepared through glow discharge electrolysis plasma (GDEP). The experimental apparatus of the GDEP is shown in Fig. 2. The effect of different discharge voltages on the temperature and pH response performance of reed hemicellulose-based hydrogels was inspected by Zhang et al., and the formation mechanism and deswelling behaviors of reed hemicellulose-based hydrogels were also discussed. In this research, hemicellulose as backbone, hydroxyl radicals which were produced by GDEP as initiators, acrylic acid (AA) and *N*-isopropyl acrylamide (NIPAAm) as monomers, and *N*,*N*-methylene double acrylamide (MBA) as cross-linking agents have been used to prepare temperature/pH dual sensitivity reed hemicellulose-based hydrogel. It turned out to be that all reed hemicellulose-based hydrogels had a double sensitivity to temperature and pH, and their phase transition temperatures were all approximately 33 °C, as well as the deswelling dynamics met the first model. In addition, the prepared hydrogel in this research, under discharge voltage 600 V, was more sensitive to temperature and pH and had higher deswelling ratio. In the process of glow discharge, joule heat, produced by electric current, makes the solution vaporize gas sheath around the electrodes rapidly. When the discharge voltage is high, gas water vapor molecules in the gas sheath layer produce sustained plasma. Many highly active components within plasma such as $HO^{\bullet}$ and $H^{\bullet}$ distributed in solution provide reactive intermediate source for solution chemistry reaction. The hydrogen of the hemicellulose

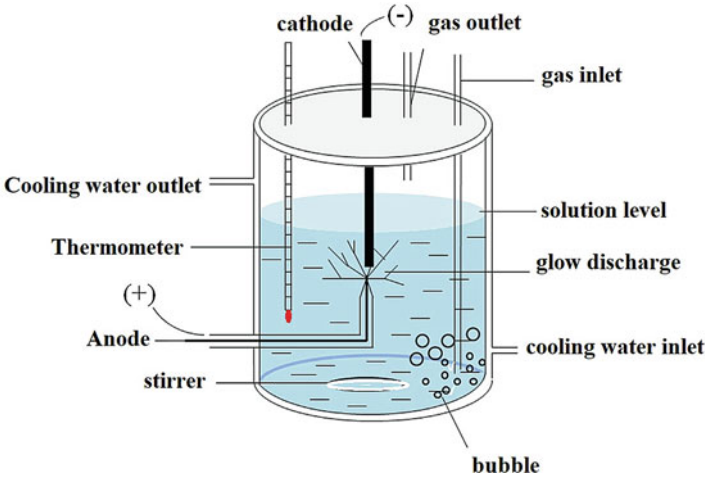

Fig. 2 The experimental apparatus of the glow discharge electrolysis plasma [6]

hydroxyl groups is seized by highly active components for the purpose of making it a main chain with active free radicals. What is more, the copolymerization with acrylic acid (AA) and *N*-propyl acrylamide (NIPAAm) eventually occurs in the solutions, and the three-dimensional network structure of reed hemicellulose-based hydrogel is obtained [6].

Glow discharge electrolysis plasma (GDEP) is emerging as a potential alternative to conventional technologies for the formation of hydrogels due to its low costs, high efficiency, easy operation, and mild reaction conditions. GDEP is a kind of non-faradaic electrochemical process and exhibits the characteristics of non-faraday, which produces numerous highly active particles in plasma electrolysis, such as $HO^{\bullet}$, $H^{\bullet}$, $HO_2^{\bullet}$, e_{aq}^{-}, and $H_2O_2^{\bullet}$. The yield of HO is more than 12 mol per mol electron of electricity in the process of glow discharge electrolysis, which suggests that GDEP is a rich source of free radical in aqueous solution and can be applied to induce some unusual chemical reactions by taking place of chemical initiator in solution. In recent years, a series of adsorbing composites were prepared by GDEP technology and showed some excellent properties. However, there were few studies directly on the preparation of cellulose-based hydrogels with multi-stimulus response properties by GDEP technology. Novel ionic hydrogels have been prepared successfully from cellulose in the NaOH/urea aqueous system by a glow discharge electrolysis plasma (GDEP) technique by Zhang and his coworkers. The results showed that the swelling behavior and the network structure of the ionic hydrogels could be controlled by changing discharge voltage or discharge time, whereas we obtained the maximum absorbency of 898 g g^{-1} for distilled water at 570 V and 90 s. Shrinkage of the network hydrogels took place at higher or lower pH. Relative to the Na^{+} buffer solution, hydrogels were more sensitive to Zn^{2+} and Fe^{3+} buffer solutions and showed network shrinkage and lower swelling ratio. In Na^{+} ionic solution, the swelling ratios of hydrogels are higher and more different. This work provided a new pathway for preparation of cellulose-based hydrogels with environmental friendliness, high water absorption capacity, and rapid and multiple responses to pH and ions, which may allow their use in the biomaterial area [27].

8 Gamma Irradiation of Hydrogels

In recent years there has been a growing interest in hydrogel systems prepared by gamma-ray irradiation. Gamma-ray irradiation is an available technique for the modification of the chemical and physical properties of polymeric materials. The gamma-ray irradiation method has advantages, such as relatively simple manipulation without the need of any extra agents for polymerization and cross-linking; by contrast, the thermal activation method requires radical initiators and cross-linkers. For these reasons, gamma-ray irradiation method is useful for preparing hydrogels for medical applications, for which even a small contamination is undesirable, and is often used to sterilize biomedical devices for medical and veterinary applications. Natural polysaccharides such as hyaluronic acid (HA) have been extensively studied in medical applications since they provide intrinsic biological activity when used as

basis for biomaterials. Zhao and his coworkers prepared hyaluronic acid (HA) and chondroitin sulfate (CS) and the synthetic polymer, poly (vinyl alcohol) (PVA), hydrogels using gamma irradiation. All HA/CS/PVA hydrogels showed relatively high water contents of greater than 90%. These hydrogels reached an equilibrium swelling state within 24 h [28].

Polysaccharides such as cellulose, starch, chitin/chitosan, and their water-soluble derivatives have been known as degradable-type polymers under action of ionizing radiation. However, it was reported that water-soluble polysaccharide derivatives such as carboxymethyl cellulose (CMC) would undergo radiation cross-linking in a high concentrated aqueous solution (more than 10%, paste-like state). It has been proposed that radiation formation of cross-linking of these polysaccharides was mainly due to the mobility of side chains. Side-chains radicals were formed mostly via indirect effects, by the abstraction of H atoms by the intermediate products of water radiolysis. The idea was to apply high concentrated aqueous solutions of the polymer of high degree of substitution. It was assumed that the hydrogel formation of polysaccharide derivatives by radiation was mainly due to the mobility of side chains. Side-chains radicals were formed mostly via indirect effects, by the abstraction of H atoms by the intermediate products of water radiolysis [29].

$$H_2O \xrightarrow{\text{Gamma irradiation}} e_{aq}^{-},\ OH^{\bullet},\ H^{\bullet},\ H_2O_2,\ H_2$$

Plungpongpan et al. prepared hydrogels from polymer blend between poly (*N*-vinyl pyrrolidone) (PVP) and methyl hydroxyethyl cellulose (MHEC) via gamma irradiation. The cross-linking structures in the hydrogels were induced by varying the irradiation doses from 10 to 40 kGy. The gel fraction and the swelling ratio of hydrogels were characterized. The results showed that the swelling ratio of hydrogels increases with increasing the irradiation dose [29].

In the other point of view, water sources like lakes, sea, groundwater, etc. are becoming polluted by different kinds of contaminants, including toxic heavy metals (e.g., Cr, Pb, Cu, Ni, Cd, Fe, etc.) accidentally and deliberately discharged into these surface waters by commercial and industrial establishments. The resulting environmental hazards are undesirable, and therefore heavy metal ions must be appropriately removed using new/improved techniques. In a novel research work, sodium carboxymethyl cellulose (CMC Na)/sodium styrene sulfonate (SSS) hydrogels with grafted and cross-linked polymeric networks were prepared by gamma radiation at atmosphere condition (Fig. 3). The metal ion adsorption capacity of CMC/SSS gel was investigated. The grafted gel effectively removed metal ions, especially Cr and Pb [30].

In similar research work, thermo- and pH-sensitive Ag-P(NiPAAm/IA) hydrogel nanocomposites were prepared by in situ reduction of Ag^{+} ions with gamma irradiation [31].

Also, Yang et al. prepared inorganic/organic hybrid poly (*N*-isopropylacrylamide) (PNIPAM) hydrogels based on polyhedral oligomeric silsesquioxanes (POSS) via gamma-ray irradiation in one step. The swelling and deswelling behavior of PNIPAM

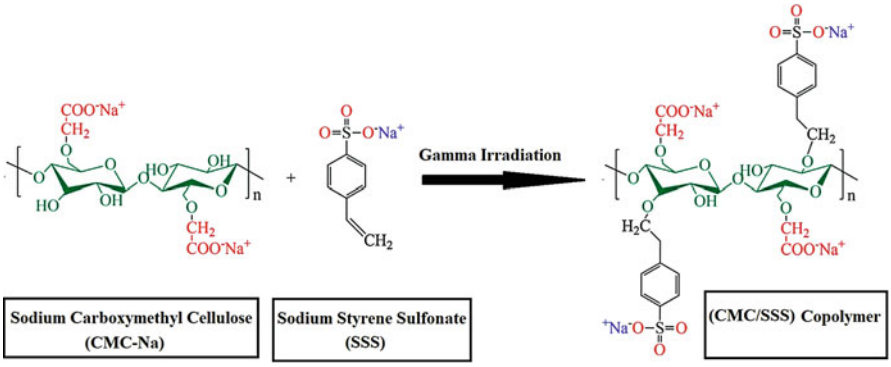

Fig. 3 A brief proposed mechanism for induced grafting of SSS onto CMC [30]

hydrogels indicated that POSS-containing hydrogels had a good water absorption capability and rapid water release capability. Thus, these thermal-responsive POSS-containing hydrogels would have some potential applications such as biological fields [32].

In similar research, gamma irradiation synthesis of silver/poly(vinyl alcohol) (Ag/PVA) hydrogels has been carried out by exposing the mixture of PVA and $AgNO_3$ in double-distilled water to gamma irradiation for 25 kGy dose. The swelling properties of the Ag/PVA hydrogel were compared with the PVA hydrogel by Swaroop et al. Significant increase in the swelling percentage of Ag/PVA hydrogel was observed in comparison to PVA hydrogel [33].

Application of polymers cross-linked by gamma irradiation on cutaneous wounds has resulted in the improvement of healing. Chitosan (CH)- and poloxamer 407 (P407)-based hydrogels confer different advantages in wound management. To combine the properties of both compounds, a gamma-irradiated mixture of 0.75/25% (w/w) CH and P407, respectively, has been obtained. Its thermo-reversibility and gelation properties at a low temperature allow for easy application to the wound, while the ability to swell in the presence of human serum permits the control of excessive exudate for skin wound application [34].

In similar research, poly(vinyl pyrrolidone) (PVP), poly(ethylene glycol) (PEG), and agar have been used for preparing wound dressing under gamma irradiation [35].

If a biomaterial is to be implanted in the body, it must be subjected to a sterilization procedure which often involves gamma irradiation. Magda et al. reported results for the effects of gamma irradiation on the glucose response of a hydrogel with glucose-binding boronic acid moieties. This "smart" hydrogel is of a type suitable for use in nonenzymatic glucose sensors. Exposure to gamma rays reduces the glucose-response sensitivity by over 50%, possibly due to the formation of additional hydrogel cross-links [36].

In the other research, interpenetrating network based on poly(acrylamide-aniline)-grafted gum ghatti has been synthesized under gamma irradiation using

N,*N*′-methylenebis-acrylamide (MBA). The optimum grafting was observed when the reaction mixture containing 10 ml solvent, 0.324×10^{-1} molL^{-1} MBA, and 1.08 molL^{-1} monomer was exposed to 1.5 kGy dose of gamma radiation. The electrical conductivity of doped IPN structures increased with an increased concentration of HCl. However, a high concentration of HCl led to a decrease in electrical conductivity, which may be due to the over protonation of PANI chains in the cross-linked networks [37].

A network of covalently cross-linked wax hydrogel bearing acidic and amide groups using gamma irradiation has been successfully developed by Ghobashy et al. He found that it has a promising application in dye removal [38].

9 Effect of Electron Beam on Hydrogels

Electron beam cross-linking is a clean and safe technology, especially for biomedical application, since it does not require any external initiators and cross-linkers. The irradiation-induced cross-linking technique provides sterilization and hydrogel cross-linking in a single step. The physical properties of hydrogels produced in this manner are dependent on the degree of cross-linking and polymer composition. This method also provides an alternative to the use of chemical initiators and cross-linkers, which can be harmful and difficult to remove. Recently bacterial cellulose/acrylic acid (BC/AA) hydrogels synthesized by electron beam irradiation and investigate its wound healing potential in an animal model. Vivo experiments indicated that hydrogels promoted faster wound healing, enhanced epithelialization, and accelerated fibroblast proliferation compared to that in the control group. These results suggest that BC/AA hydrogels are promising materials for burn dressings [39, 40].

In the other research, electron beam irradiation has been applied to prepare a chemically cross-linked hydrogel based on tyramine conjugated gum tragacanth. The gel content of the prepared hydrogels was in the range of 75–85%. Equilibrium swelling degree of the hydrogels decreased from 51 to 14 with increasing polymer concentration and irradiation dose. Moisture retention capability of the hydrogels after 5 h incubation at 37 °C was in the range of 45–52 that is comparable with that of commercial hydrogels. The cytotoxicity analysis showed the good biocompatibility of hydrogels. These results indicated that electron beam irradiation is a promising method to prepare chemically cross-linked tyramine conjugated gum tragacanth hydrogels for biomedical applications. Also, the versatility of electron beam irradiation for cross-linking of a variety of polymers possessing tyramine groups was demonstrated [41].

In the other research, Choi and his coworkers prepared eggshell membrane (ESM)-based hydrogel by incorporating with polyvinyl alcohol (PVA) via an electron beam irradiation technique. Hen egg shell membrane (ESM) is an abundant natural protein resource and can be readily obtained almost anywhere as a waste. ESM is a thin, highly collagenized fibrous membrane formed by types I, V, and X collagen, making up 88–96% of its dry weight. It has been used as a biomaterial, particularly as a matrix for absorption of heavy metal ions, a template for the formation of ordered

tube networks, a platform for enzyme immobilization, and a scaffold material for tissue engineering. The internal 3D porous network structure, the high absorption capacity, and the possible microbial sterilization due to EBI are the main features of the introduced hydrogel, which make it a suitable candidate for biomedical applications such as wound dressing, drug delivery, tissue scaffolds, etc. More importantly, the preparation strategy could be considered as a cost-effective method which could eliminate the use of toxic chemicals to prepare hydrogel for biomedical applications. We hope, this method can be extended to fabricate a variety of polymer hydrogels for different applications [42].

In similar research, the temperature- and pH-responsive characters of hydrogels prepared from aqueous solutions containing 4.2% and 25% (w/v) carboxymethyl cellulose (CMC) and acrylic acid (AAc), respectively, under the effect of accelerated electrons was investigated. Even though the initial content of hydrogel solution is constant, the swelling in water and responsive characters was greatly dependent on electron beam irradiation dose. In this regard, the percentage swelling in water of the hydrogel prepared at 50 kGy is relatively higher than that prepared at 80 kGy. However, both hydrogels displayed super water-absorbing behavior at room temperature in the range of ∼3500–4000%. The swelling of CMC/AAc hydrogel prepared at 50 kGy was found to substantially increase with increasing pH values from 3 to 10; the hydrogel prepared at 80 kGy was found to display pH-responsive character below and above 7 [43].

Park and his coworkers found that the pure keratin (human hair and wool) aqueous solution was not gelled by EBI, while the aqueous keratin solutions blended with PVA were gelled at an EBI dose of more than 90 kGy. Furthermore, in the presence of PEI, the aqueous keratin solution blended with PVA could be gelled at a considerably lower EBI dose, even at 10 kGy [44].

Blend hydrogels based on aqueous solutions of plasticized starch and different ratios of cellulose acetate (CA) and carboxymethyl cellulose (CMC) were prepared by electron beam irradiation (EB). The blends before and after EB irradiation were characterized by thermos gravimetric analysis (TGA) and differential scanning calorimetry (DSC). The physicochemical properties of blend hydrogels prepared by electron beam irradiation were improved compared to unirradiated blends [45].

10 Microwave Irradiation of Hydrogels

The microwave irradiation is one technique, which is used for preparation of the hydrogel in several researches. Microwave heating process has high temperatures for attack the solution with relatively short times and thus creates reactions faster than under conventional thermal conditions [46].

Microwave irradiation is a special heating energy, and it has some significant advantages over the conventional thermal methods in preparation of colloid particles. Omprakash used microwave irradiation followed by hydrothermal method for synthesizing ZSM-5 type of zeolite and found that zeolite synthesized by microwave irradiation method only took half the time for ZSM-5 crystallization of 100%

crystallinity to that of conventional hydrothermal heating method. Hence, microwave treatment method is economic and time saving. Li et al. used microwave irradiation synthesis method for the preparation of thermosensitive poly(*N*-isopropylacrylamide) (PNIPAAm) hydrogels. He found that the PNIPAAm hydrogels synthesized using microwave irradiation had much higher swelling ratios at 10.0 °C below the (lower critical solution temperature) LCST [47, 48].

Cross-linked acrylamide-based thermosensitive hydrogels are interesting candidates for biomedical or pharmaceutical applications, such as drug release because they change volume and expel a significant amount of its inner solution when a transition is induced by external action. These kinds of materials based on smart hydrogels could also be used in chemical or mechanical actuators as well as environment sensors for technological applications. It has been shown that the in situ polymerization water-soluble monomers (aniline or pyrrole) inside a hydrogel produce nanocomposite with conductive and dielectric domains. The nanocomposite suffers a phase transition by externally changing the temperature of the gel or by microwave absorption. Upon microwave irradiation, the conductive polymer absorbs the radiation and heats up driving the phase transition of hydrogel which involves a clear volume decrease and inner solution expulsion. It is found that the amount of water released correlates well with the surface temperature of the materials upon microwave irradiation [49].

Li et al. studied the swelling and deswelling kinetics of poly(*N*-isopropylacrylamide) (PNIPAAm) hydrogels separately synthesized by means of microwave irradiation and normal water bath heating. As compared with the PN hydrogel synthesized by the conventional method, the PM hydrogel synthesized by microwave irradiation had larger swelling and deswelling rate constants as well as lower swelling/deswelling activation energy due to its higher surface area and larger pore sizes, and thus it had faster response behavior. Also he found that the use of microwave irradiation method to prepare the hydrogel not only made it more porous but also made its pores more uniform and deeper [50].

In the other study, microwave irradiation technique has been used to synthesize poly(acrylamide-co-2-hydroxyethyl methacrylate)/poly(vinyl alcohol) (P(AM-co-HEMA)/PVA which are separately synthesized by using one-pot polymerization and two-step polymerization techniques. The hydrogel prepared by one-pot polymerization technique exhibited the highest swelling ratio and reduced step of polymerization, compared with the hydrogels prepared by two-step polymerization technique. The hydrogel of 50% HEMA-PM showed the maximum mass swelling percentage (the mass swelling percentage has higher than 900%) [46].

To prepare a novel biodegradable hydrogel for use in tissue engineering, pHEMA hydrogel has been synthesized by microwave-assisted polymerization using 2-hydroxyethyl methacrylate (HEMA) as the raw material, potassium persulfate as the initiator, and PCLX as the cross-linking additive. Biodegradation studies showed 75% uniform bulk degradation of the hydrogel over a period of 17 days. In addition, the biodegradable hydrogel had no observable cytotoxicity toward L-929 fibroblast cells. Therefore, this novel bioresorbable pHEMA can play an important role as a scaffold for tissue engineering applications [51].

11 Ultrasonication of Hydrogels

The radiation synthesis is a kind of new technology which was highly effective and eco-friendly. And because of its high temperatures for attacking the solution with relatively short times and thus creating reactions faster than conventional thermal conditions, microwave irradiation has been used for preparation of the hydrogel in several researches. Also ultrasound has been investigated for the initiation of polymerization reactions to prepare polymer hydrogel since it can be used both for dispersion of monomer droplets and for generation of free radicals. The use of ultrasonic irradiations during the hydrogel synthesis not only can control the molecular weights but also can improve the swelling ratio. Wang et al. synthesized the hydrogels based on gelatin cross-linked with chitosan (CS) and polyvinyl pyrrolidone (PVP) using microwave and ultrasonic coupling technique. This interpenetrating polymer network (IPN) hydrogels were cross-linked by glutaraldehyde and 1,2-Epoxy-4-vinylcyclohexane. The results showed that the hydrogel prepared with microwave and ultrasonic exhibited the highest tensile strength (86.68 MPa), compared with the hydrogel prepared with traditional method and only microwave reactive field. The FT-IR and XRD results showed that the chemical reactions occurred between the eNH2 of chitosan and the eCOOH of gelatin and the introduction of ultrasound can improve the reaction rate. The hydrogel film gained in microwave and ultrasonic coupling field has the best combination properties. Therefore, the new microwave-ultrasonic coupling technique is the potential technology to prepare the new hydrogel due to less synthesis time [52].

In the other research, Wang et al. successfully prepared a series of (sodium lignosulphonate) SLS-based hydrogels by ultrasonic-assisted synthesis which is green, fast, and convenient relative to other methods. The swelling capacity of SLS-based hydrogels was measured in various experimental conditions like pH, SLS content, and different electrolytes. The results demonstrated that the water uptake capacity achieved the maximum when containing 1 wt% sodium lignosulphonate. It was worth mentioning that the maximum of swelling capabilities could reach 1328 g g^{-1} and 110 g g^{-1} in deionized water and 0.9% NaCl solution, respectively. It was found through the exploration that the swelling behavior in aqueous solution was consistent with the pseudo-second-order kinetic model. At the same time, SLS-based hydrogel was selected as an adsorbent to remove Ni^{2+} from an aqueous solution, and the maximum adsorption capacity reached about 293 mg g^{-1} under the optimal experimental condition. The adsorption capability of SLS-based hydrogel was influenced by pH, temperature, and adsorption time as well as initial concentration. The mechanism of adsorption was evaluated by fitting adsorption data to different kinetic models and adsorption isotherms, and the findings revealed that the adsorption behavior was endothermic and spontaneous as well as multi-molecular layer chemisorption [53].

Nowadays adsorption of dyes is carried out with superabsorbent hydrogels due to their high water absorption property. Lignin is a biodegradable, eco-friendly, low-cost, and renewable raw material and is strongly reactive due to its aromatic nature and functional groups (carboxyl and phenol groups), which can potentially be

used for high performance as adsorbent. However, its adsorption amount and adsorption rate need to be further improved for practical applications. Ultrasound-irradiation has been investigated for the initiation of bulk polymerization reactions to produce polymer hydrogel since it can be used both for dispersion of monomer droplets and for generation of free radicals. The use of ultrasonic irradiations during the hydrogel synthesis not only can control the molecular weights which are attributed to the high shear gradients generated by cavitational events but also can improve the dispersion of the clay with enhancement in the mechanical properties and adsorption capacity of hydrogels. A novel hybrid hydrogel has been synthesized from grafting of acrylamide and *N*-isopropyl acrylamide onto lignin by incorporation of montmorillonite under ultrasonic irradiation (lignin-g-p(AM-co-NIPAM)/MMT). This hydrogel was employed for the removal of methylene blue from the aqueous solution, and it exhibited good swelling-deswelling property. The initial swelling kinetic was Fickian-type diffusion, and the whole swelling process was good fit for Schott's pseudo-second-order model. The adsorption process was found to be highly pH and temperature dependent and followed the pseudo-second-order rate model [54].

In the other research, hen egg white lysozyme (LZM) cross-linked with ultrasonic-treated tragacanth (US-treated TGC) under mild Maillard reaction conditions. Since this gum is extensively used in food industry and application of LZM as a natural antimicrobial agent in different food systems is recommended and practiced in some countries, the results of this study indicate that a conjugated product of these two polymers combines different properties into one macromolecule and improves the property of each. These properties may make the conjugate an attractive food ingredient [55].

Ultrasonic radiation is used in a vast range of applications. More commonly this includes imaging (industrial and medical), physiotherapy, and welding of metals and plastics. High frequencies are commonly used for imaging, whereas low frequencies (less than 500 kHz) provide strong physical and chemical interaction with materials. The physical effects of low-frequency (high power) ultrasound include high shear rates, free radical production in solution, and heat generation. This has been utilized for fragmentation and dissolution of solids, biological techniques, the preparation of nanomaterials, various synthetic sonochemical reactions, thermal applications such as plastic welding, and environment remediation. Ultrasound has also been investigated for many polymer-based applications. These include polymer synthesis through the generation of free radicals, activation of free radical initiators, degradation of polymers in solution by high shear rates, and physical mixing of heterogeneous emulsion/suspension polymerization systems. Several acrylic hydrogels have been prepared via ultrasonic polymerization of water-soluble monomers and macromonomers by Cass et al. Ultrasound was used to create initiating radicals in viscous aqueous monomer solutions using the additives glycerol, sorbitol, or glucose in an open system at 37 °C.

Ultrasound was found to be an effective method for the polymerization of water-soluble vinyl monomers and for the production of hydrogels. This occurs rapidly in the absence of a chemical initiator. The water-soluble additive was essential for the

preparation of hydrogel. We propose that its effect is attributed to the enhanced viscosity increasing the free radical production as well as reducing the polymer solubility and hence retarding depolymerization. The most effective additive for the preparation of hydrogels was glycerol. Such a technique may find application in the field of biomaterial synthesis to avoid problems associated with cytotoxic initiators. In combination with techniques such as high intensity focused ultrasound, the polymerization method described here may also allow the formation of hydrogels in vivo [56].

12 Conclusion

Without a doubt, there are a number of significant features of hydrogels that qualify and allow them to exhibit extraordinary characteristics, which enables them to be employed as essential tools for applications in almost all the fields, such as biomedical, agricultural, industrial, and environmental areas. From time to time, significant modifications are made to revolutionize the field of hydrogels for their comprehensive applications. Nowadays, smart and electrical conductive hydrogels play very important role in different branches of industry. Although extensive research is ongoing in order to provide new kind of hydrogels for future necessities, novel conceptual assimilation of hydrogel preparation such as different irradiation methods may lead to tailored properties, translating its innovative applications in the diversified fields. Above all, an economical way to improve the efficacy of the hydrogel system will be the most demandingly needed approach.

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Cellulose-Based Composite Hydrogels: Preparation, Structures, and Applications

21

Liying Qian

Contents

Abstract

In this chapter, cellulose-based composite hydrogels were summarized in three categories according to the components. Synthetic polymer/cellulose composite hydrogels combine the advantages of synthetic polymers and cellulose. Soluble cellulose derivatives are feasible to construct the composite hydrogels with polyacrylamide, polyvinyl alcohol, polyacrylic acid, and so on. The composite hydrogels are normally applied as superabsorbents for heavy metal ions and dyes because the abundant functional groups in the hydrogels can act as binding sites. Due to most of the crosslinked polymeric hydrogels suffering from poor

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mechanical performance, low breaking strain, and sensitivity to fracture, cellulose nanocrystal can be combined into the hydrogels to enhance the mechanical properties significantly in order to obtain the mechanically strong, tough, or highly stretchable nanocomposite hydrogels. Natural macromolecules/cellulose composite hydrogels have a great potential for applications in tissue engineering, drug delivery, sensors, and purification for their excellent biocompatible, biodegradable, and nontoxic properties. Cellulose hydrogels have high mechanical strength and good permeability for liquids, gases, and electrolytes, the composite hydrogels which combine cellulose and extracellular matrixes are very promising scaf folds for the tissue repair and regeneration. Chitosan, alginate, and other polysaccharides are popular natural macromolecules for the composite hydrogels. Inorganics/cellulose composite hydrogels have recently received considerable attentions in both academic research and industrial application due to their excellent hybrid properties. Montmorillonite, clay, and bentonite are traditional inorganic minerals to fabricate the composite hydrogels as superabsorbents for water treatment, personal care, and agriculture. Nanoparticles of ZnO and Ag are also incorporated into the cellulose hydrogels to render the antimicrobial activity to biomedical materials. Recently, the novel cellulose-based composite hydrogels with graphene oxide, carbon nanotube, and carbon dots show potential applications in supercapacitors and biosensors.

Keywords
Composite hydrogel · Synthetic polymer · Natural macromolecules · Inorganic; Preparation · Structures and applications

1 Introduction

Cellulose composite hydrogels can be prepared from cellulose and macromolecules or inorganic materials with physical and chemical crosslinking. Physical hydrogels are formed by molecular self-assembly through ionic or hydrogen bonds, while chemical hydrogels are formed by covalent bonds [1]. Cellulose can take part in the formation of 3D network or act as reinforcement. Interpenetrating polymer networks (IPNs) are common structures for cellulose-based composite hydrogels, especially for synthetic polymer/cellulose composite hydrogels. IPNs can be divided into two types: sequential IPN and semi-IPN. For sequential IPN, cellulose is used as the first network, and the second network is formed by polymerizing in the presence of the cellulose network. When cellulose or its derivative is linear or branched in a crosslinked network, it is called as semi-IPN hydrogel [2]. Nanocellulose is an excellent reinforcement for both synthetic polymer and natural macromolecule hydrogels. Inorganic/cellulose composite hydrogels combine the advantages of both components which are very promising materials in biomedicals, tissue scaffold engineering, superabsorbent, and so on. The main purposes of incorporation of inorganics are reducing production cost, improving the properties, and rendering special features. This chapter discusses about cellulose-based composite hydrogels

including synthetic polymer/cellulose, natural macromolecules/cellulose, and inorganics/cellulose composite hydrogels with the emphasis on the latter two categories.

2 Synthetic Polymer/Cellulose Composite Hydrogels

2.1 Water-Soluble Cellulose Derivatives

Naturally available cellulose is not water-soluble due to the hydrogen bonding between molecular chains; the strong intermolecular and intramolecular hydrogen bonds between the hydroxyl groups not only limit the water solubility but also lead to the poor reactivity of cellulose. However, water-soluble cellulose can be prepared by esterification and etherification reaction of the hydroxyl groups. Methyl cellulose (MC), hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose (HPMC), and carboxymethyl cellulose (CMC) are common water-soluble cellulose derivatives. The concentrated aqueous solution of cellulose derivatives can be crosslinked under irradiation to prepare cellulose-based hydrogels [3]. It is feasible to incorporate some synthetic polymers with cellulose to fabricate the composite hydrogels by chemical crosslinking via crosslinker and irradiation, physical crosslinking, and ionic crosslinking.

CMC is a representative cellulose derivative, which is manufactured by reacting sodium monochloroacetate with cellulose in alkaline medium. It is the most popular cellulose derivative to prepare the composite hydrogels with synthetic polymers. In situ free-radical solution polymerization of acrylate monomers onto CMC is one of main methods to introduce synthetic polymers into CMC hydrogels. By this method, acrylic acid (AA) [4–6], acrylamide (AM), and N-isopropylacrylamide (NIPAM) can be grafting polymerized on CMC and chemically crosslinked to the composite hydrogels by chemical crosslinker [7, 8] or irradiation [9–11]. Methylenebis acrylamide (MBA) always acts as a chemical crosslinker or a crosslinking enhancer agent in irradiation [12–15]. Polyacrylic acid (PAA)/cellulose composite hydrogels have been widely reported for the applications of drug delivery and adsorbent. The negative carboxyl groups in PAA/CMC composite hydrogels facilitated the removal of cationic dyes via electrostatic interactions [16]. Cyclodextrin (CD) and CMC were grafting polymerized with AA to prepare CD/CMC-g-PAA hydrogels with pH sensitive as drug delivery system [17, 18]. A double crosslinking PAA hydrogel via visible-light-trigger polymerization, with CMC as initiator and the first crosslinker and MBA as the second crosslinker, showed a remarkably rapid recovery in both successive and intermittent cyclic tensile tests [19]. Hydrogels based on AM monomer and CMC were synthesized by gamma irradiation with MBA as a crosslinking enhancer agent for drug release system [20] and agrochemicals [21]. Interpenetrating double network was formed by chemically crosslinked polyacrylamide (PAM) network and physically crosslinked CMC network (Fig. 1). This shape memory hydrogels exhibited excellent tunable mechanical properties [22], which are similar to PAA/CMC composite hydrogels [19]. Both AM and AA were grafted onto CMC and further ionic coordinated to fabricate a tough hydrogel actuator with

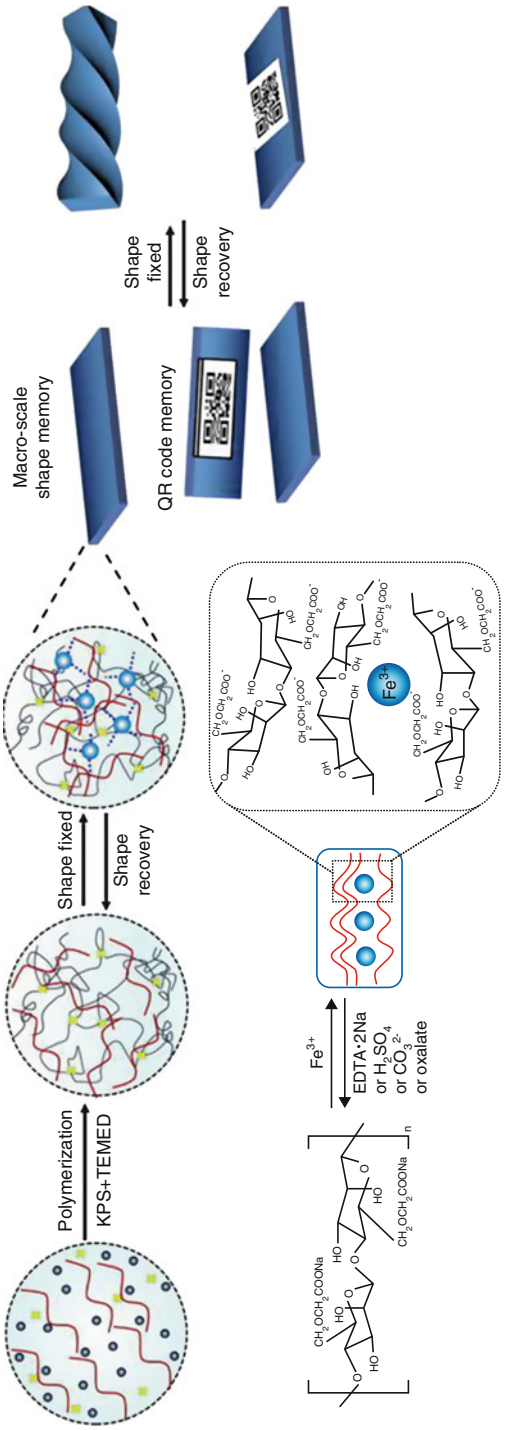

Fig. 1 Scheme of PAM/CMC hydrogels with excellent shape memory effect. (Reproduced from [22])

programmable folding deformation which showed great application prospect in soft machine. The ionic coordination was utilized to not only trigger the locally folding deformation of the hydrogels but also reinforce the mechanical property significantly [23]. By grafting poly(N-isopropylacrylamide) (PNIPAM) onto CMC, the self-association of grafted chains led to a thermothickening effect compared to the physical blends [24]. PNIPAM/CMC composite hydrogels with thermo- and pH responses are promising materials for protein and drug delivery [25, 26]. pH, thermo-, and redox ternary-responsive composite hydrogels were prepared by free-radical polymerization using methacrylated carboxymethyl cellulose (MACMC) and NIPAM as monomers [27]. PNIPAM and CMC were functionalized with hydrazide or aldehyde functional groups and mixed using a double-barreled syringe to create in situ gelling and hydrazone-crosslinked composite hydrogels, which provided a highly adaptable method of engineering injectable, rapidly gelling hydrogels for potential in vivo applications [28]. CMC can also be incorporated with some synthetic polymers to fabricate the composite hydrogels for medical and super-absorbent applications [29, 30].

MC is normally obtained by heating cellulose with a solution of sodium hydroxide and methyl chloride to replace the hydroxyl groups of cellulose by methoxyl groups. MC can form a thermoreversible physical hydrogel itself. At low temperatures, the hydrogen bonds formed and the polar water molecules form cages around the hydrophobic methoxyl groups of MC; upon heating, the hydrogen bonds and the water cages were broken to expose the hydrophobic side groups of MC chains, inducing hydrophobic associations and thus gelation [31]. MC-based injectable hydrogels for postoperation anti-adhesion were fabricated by mixing CMC, polyethylene glycol (PEG), and chitosan sulfate (CS-SO_3) in the MC matrix with a low critical solution temperature (LCST) at 36 °C [32]. PAM/MC/montmorillonite (MMT) composite hydrogels were obtained through chemical polymerization of the AM monomer in aqueous solution containing MC and MMT which were appropriate for the controlled release of fertilizers with very high fertilizer loading in their structures [33]. PAM/MC semi-IPNs composite hydrogels were prepared by aqueous radical polymerization at room temperature, and MBA was used as a crossliking agent [34, 35]. Frontal polymerization (FP) was exploited as an alternative and convenient technique to prepare PAM/MC composite hydrogels swollen either in water or glycerol [36]. MC was modified with functional methacrylate groups and photocrosslinked to produce hydrogels for potential applications in plastic and reconstructive surgery [37]. Polythiophene-g-poly(dimethylaminoethyl methacrylate)-doped MC hydrogel behaved like a polymeric AND logic gate [38].

HPMC is produced by the addition of methyl and hydroxypropyl groups to the cellulose backbone. PAM/HPMC composite hydrogels were synthesized by radical polymerization technique which demonstrated controlled drug release behavior due to the hydrophobicity as well as lower rate of erosion [39, 40]. Thermosensitive PNIPAM/HPMC hydrogels were prepared, and swelling ratio of the hydrogel decreased with increasing temperature [41]. HPMC hydrogels containing PEG as crosslinks were prepared by reacting HPMC with polyethylene glycol dichloride which was a promising drug delivery system for the drugs to be delivered to the colon [42].

HEC is obtained by reacting cellulose with sodium hydroxide, and hydroxyl groups of cellulose are replaced by hydroxyethyl groups. Double-layered gels, consisting of HEC cryogel core and poly(ethylene oxide) (PEO) hydrogel shell, were synthesized with UV irradiation which were used as carriers for immobilization by entrapment of cells [43]. Composite hydrogels from poly(N-vinyl pyrrolidone) (PVP) and methyl hydroxyethyl cellulose (MHEC) were obtained via gamma irradiation [44]. PAA/HEC composite hydrogels were prepared by in situ method, and moduli of the composite hydrogels were improved dramatically compared to HEC [45]. HEC-g-PAA/vermiculite superabsorbent nanocomposites were prepared by radical solution polymerization among HEC, AA, and vermiculite in the presence of MBA as crosslinker [46]. PNIPAM/HEC composite hydrogels were prepared by copolymerization with NIPAM onto HEC, and LCST of hydrogels was enhanced by the introduction of HEC [47].

HPC is synthesized by chemical modification of cellulose with an etherifying agent, propylene oxide, which results in the introduction of hydroxypropyl side chains onto cellulose chains. Composite hydrogels with HPC and two methacrylate compounds were obtained by irradiation with γ-rays. Radiation-induced change of optical properties made them to be good candidates of a new type of radiation dosimeter utilized in radiation therapy [48]. Thermally sensitive hydrogels were prepared by crosslinking HPC with polyethylene glycol diglycidyl ether which swelled at low temperature and contracted at high temperature [49]. Ternary system thermoresponsive hydrogels, poly(N-isopropylacrylamide-co-hydroxyethyl methylacrylate polycaprolactone)/HPC (P(NIPAM-co-HEMAPCL)/HPC), were prepared via "alkynyl/azide" click chemistry between the azide-modified graft copolymer P(NIPAM-co-HEMAPCL-N3) and the alkynyl-modified HPC (Fig. 2). The composite hydrogels exhibited reversible swelling-deswelling behavior after three "swelling-deswelling" cycles [50]. Comb-shaped copolymer composed of HPC backbones and low-molecular-weight PNIPAM side chains were prepared via atom transfer radical polymerization (ATRP) for smart hydrogels in biomedical applications [51]. Methacrylic anhydride/HPC (MA/HPC) composite hydrogels for adipose tissue engineering applications were prepared and made to be biocompatible to human adipose-derived stem cells [52]. PAM/HPC composite hydrogels were prepared by in situ graft polymerization for heavy metal removal due to the capacity of both chemicals for forming chelates with metals [53]. PAA/HPC composite hydrogels were also fabricated via free-radical polymerization as absorbent, and a phase separation was revealed in the hydrogels [54].

2.2 Nanocellulose

Nanocellulose (NC) with high aspect ratio is partially to fully crystalline and exhibits impressive mechanical properties and tunable surface chemistries. Recently, the use of NC as a reinforcing agent for hydrogels has attracted significant research interest, especially in applications of tissue engineering scaffolds, wound healing materials, and drug delivery systems. There are three main reasons for the improved

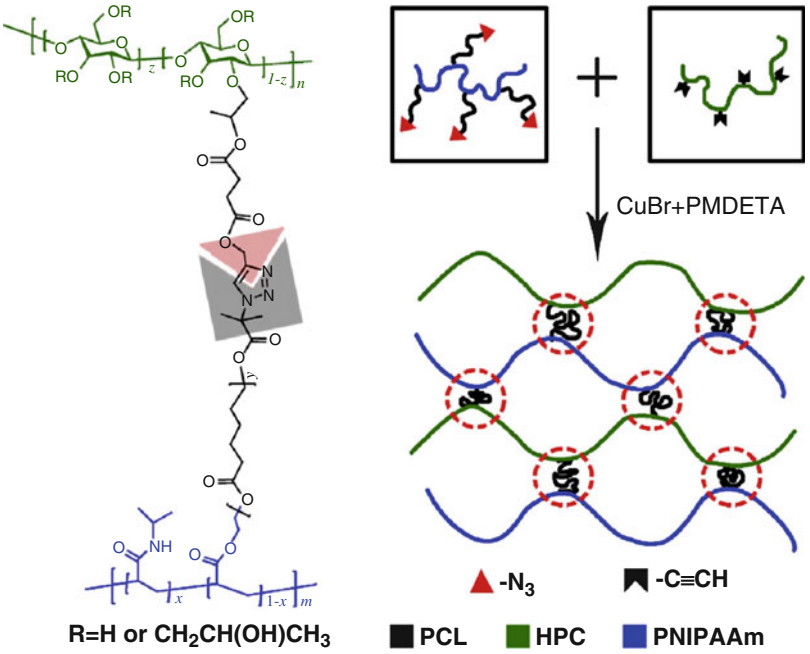

Fig. 2 Preparation of the P(NIPAM-co-HEMAPCL)/HPC hydrogels via click chemistry [50]

performance of the polymer hydrogels by incorporating NC, i.e., increased relative surface area (aspect ratios) and its associated quantum effects exhibited by NC, which formed polymer-filler interactions such as hydrogen bond, enhanced the elastic modulus with the rigid nanofibrils [55]. NC can be physically entrapped in the polymer network as a filler or chemically crosslinked with the polymer matrix in the composite hydrogels. Due to their rigidity and mechanical strength, NC acts as effective fillers in the composite hydrogels, and the majority of the NC composite hydrogel research has focused on the physical incorporation of NC as fillers. Common preparation methods include simple homogenization and physical entanglement of polymer networks, free-radical polymerization of polymeric species within NC suspensions, and UV/ion-mediated crosslinking of the polymeric network around the NC and cyclic freeze-thaw processing [56].

Incorporation of NC into synthetic polymer hydrogels can significantly improve the degradation and the mechanical strength of the hydrogels. The orientation of the reinforcing NC from the anisotropic to highly isotropic state under applied stress is the main mechanism of strain-dependent behavior of the composite hydrogels [57]. Polyvinyl alcohol (PVA) is among the most promising polymer candidates for the composite hydrogels because it is biocompatible, nontoxic, and readily crosslinked polymer. With the increase of NC concentration in PVA hydrogels, the composite hydrogels greatly improved the mechanical strength while maintaining remarkable ductility [58, 59]. PVA/NC composite hydrogels obtained by freezing-thawing (F-T)

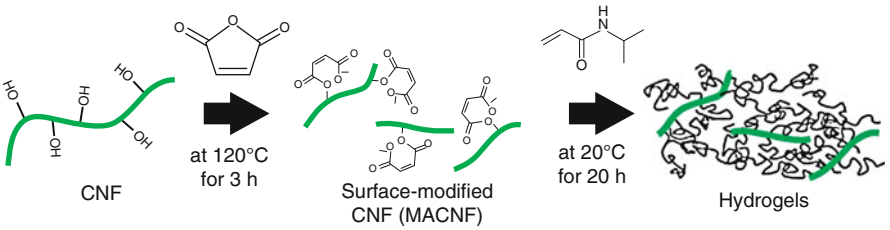

Fig. 3 Surface modification of NC with MA and the following hydrogel formation via in situ polymerization of NIPAM [71]

technique revealed increased thermal stability, mechanical properties [60], and proper water vapor transmission rate in the potential application of wound dressing [61]. The porous structure of PVA/NC hydrogels can be controlled by adding PEG with various molecular weights [62]. Hyperelastic, rubberlike PVA/NC composite hydrogels mimicking collagenous soft tissues are promising materials for ophthalmic applications [57, 63, 64]. The stiffness of PVA/NC composite hydrogels was significantly enhanced by utilizing three-component recognition-driven supramolecular crosslinks [65]. NC can also be chemically crosslinked with PVA to obtain the composite hydrogels [66, 67]. NC can be incorporated into PVA/chitosan [68] or PVA/alginate [69] to form the ternary composite hydrogels.

PNIPAM is a thermoresponsive polymer and has a LCST very close to the human physiological temperature. Incorporation of NC into PNIPAM hydrogels could obtain stimuli-responsive composite hydrogels which are promising in drug delivery. PNIPAM/NC composite hydrogels obtained by in situ radical polymerization of NIPAM monomer on the surface of modified NC (Fig. 3) could be elastically stretched to more than 700 times their original length [70] which attributed to the sustainer effect of the highly aligned NC fibers in the stretched hydrogels [71]. MBA was used to crosslink NC with PNIPAM by concurrent free-radical polymerization of monomers [72–75]. Additionally, the negatively charged carboxylate groups on oxidized NC would favorably interact with hydrophilic amide groups in PNIPAM to form the network structure. AM, AA, and HEMA are common monomers to fabricate the PAM/NC [76–85], PAA/NC [86–89], and PHEMA/NC [90–92] composite hydrogels via in situ polymerization of monomers in the presence of NC.

3 Natural Macromolecules/Cellulose Composite Hydrogels

3.1 Polysaccharides

3.1.1 Chitosan

Chitosan is a linear copolymer obtained by deacetylation of chitin, and it is a polycation that has one amino group in the repeating glucosidic residue. The backbone of chitosan is very similar to cellulose excepted that some amino groups replace the hydroxyl groups on the C2 position. Chitosan is the most important

polysaccharide which incorporated with cellulose to form the composite hydrogels with many applications. The chemical crosslinking is assuredly a highly versatile method to create chitosan/cellulose composite hydrogels with stable structure and effective swelling. According to the mechanism, crosslinking reactions between chitosan and cellulose can be classified into two types: (1) crosslinking with crosslinkers such as epichlorohydrin (ECH) and ethylene glycol diglycidyl ether (EGDE) and (2) crosslinking by the reactive groups in chitosan and cellulose or their derivatives. Chemical crosslinkers form covalent bonds and link chitosan with cellulose into network. ECH is a common etherifying crosslinker resulting in formation of ROR bonds. Etherification generally involves reactions in aqueous alkaline conditions (alkali catalysis) for the deprotonation of hydroxyl groups in order to make them highly nucleophilic and reactive with the crosslinker [93]. HEC and cationic modified chitosan can be crosslinked by ECH to prepare a double-network structure for loading anionic modified β-cyclodextrin (β-CD) via electrostatic interaction (Fig. 4). Incorporation of β-CD not only increased the mechanical strength of the composite hydrogels but also encapsulated hydrophobic guest substances by the host-guest interaction, and guest molecules could adsorb rapidly in the composite hydrogels and sustain the release in aqueous solution [94]. A water-soluble hydroxyethyl chitosan and cellulose were employed to fabricate the composite hydrogel scaffolds with bubble-like porous structure by a combination of chemical crosslinking with ECH, particle-leaching technique using silicon dioxide particles as porogen, and freeze-drying method. ECH mediated the chemical reactions between the hydroxyethyl or amino groups of chitosan and the hydroxyl groups of cellulose. The compressive modulus, equilibrium swelling ratio, and elasticity of the composite hydrogels were improved. In vitro biocompatibility evaluation demonstrated that the composite scaffolds could well support the attachment spreading, viability, and proliferation of cells [95]. EGDE with double epoxide groups was used to obtain the composite hydrogels with significant improved mechanical strength and chemical stability. The chitosan/cellulose composite hydrogel beads had high adsorption capacities for Cu removal which mainly involved the nitrogen atoms in chitosan to form surface complexes [96]. Thiourea-formaldehyde resin crosslinked chitosan and cellulose firstly, and AA was grafting polymerized on the composite hydrogels to obtain the superabsorbent in controlled release of soil nutrients [97]. Genipin, a biobased crosslinker, was used to crosslink amino groups of chitosan in the presence of CMC in order to form stable nanoparticles with semi-IPN

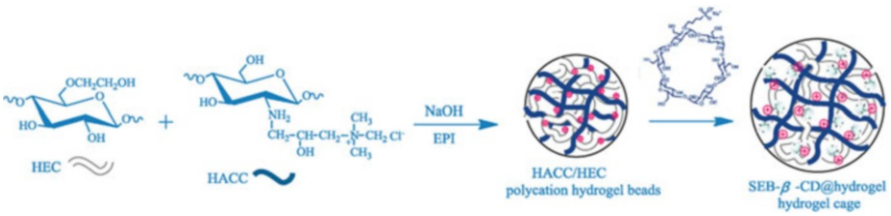

Fig. 4 The synthetic route of SEB-β-CD at hydrogel beads. (Reproduced from [94])

structure, and magnetite was lastly synthesized within the composite particles by the coprecipitation method to obtain hybrid nanoparticles which exhibited the responsiveness to a magnetic field [98].

There are an abundance of amino groups in chitosan molecules, and they are feasible to react with aldehyde groups in oxidized cellulose derivatives to form a Schiff base which is an important chemical crosslinking to produce chitosan/cellulose composite hydrogels. Sodium periodate is a normal agent to cleave the C2-C3 bond of the anhydroglucose unit in cellulose and results in the formation of two aldehyde groups. Hydrogen peroxide was also used as an oxidant which oxidized CMC in the presence of sulfate copper, and the amount of aldehydes increased with the $CuSO_4$ [99]. Due to the good water solubility, CMC was extensively employed to be oxidized to dialdehyde carboxymethylcellulose (DCMC) and self-crosslinked with chitosan or its derivatives based on Schiff base formation [100–103]. The chitosan/DCMC composite hydrogels displayed significantly better thermostability, swelling capacity, and cytocompatibility compared with glutaraldehyde (GA) crosslinked carboxymethyl chitosan [100]. Chitosan/cellulose composite hydrogels with gelation driven by Schiff base reactions are highly porous materials which are capable of loading various potential therapeutic agents including cells, drugs, and growth factors, as drug delivery carriers of an anticancer drug, drug loading and releasing can be easily modulated by tuning the composition of the composite hydrogels. Protonation of carboxylic groups in the microsphere matrix at acidic conditions resulted in an accelerated release of doxorubicin, which is desired for treating tumors [101]. Chemical stability of the composite hydrogels was improved remarkably by grafting chitosan onto cellulose hydrogels prepared by dissolution-regeneration in LiOH/urea [104].

Irradiation is a useful method for the formation of covalent bonding between chitosan and cellulose to obtain the composite hydrogels. The advantages of this method are high purity of the hydrogel products without crosslinkers and tedious process to prepare polymer derivatives. High concentrated paste-like condition was favorable for irradiation crosslinking of chitosan or cellulose; meanwhile, degradation of the polymer chains competed with crosslinking during irradiation [105]. Carboxymethyl chitosan/CMC composite hydrogels were prepared by γ-irradiation of a high concentrated mixture solution revealing the high-adsorption capacities for metal ions. It was found that the maximum strength depended on the composition of the composite hydrogels. The behavior of the tensile strength of the composite hydrogels with increasing dose was similar to that of pure hydrogels [106–108]. Additionally, MBA as a radical crosslinker could be added to the mixed solution before irradiation to enhance the gelation efficiency [109]. It was reported that macroradicals emerged preferentially in weakened C1 and C4 positions of cellulose as a result of the fracture of C-H bonds upon irradiation, while macroradicals of the derivatives were created in the side chains during radical crosslinking [110, 111].

Chitosan/cellulose composite hydrogels can be fabricated by physical interactions as well such as hydrogen bonds, electronic or hydrophobic associations, chain entanglements, and van der Waals forces. Cellulose ethers such as MC, HEC, and HPMC are the most important water-soluble derivatives of cellulose which can form

physical crosslinking composite hydrogels with chitosan via hydrophobic associations and hydrogen bonding. HPMC and MC are temperature-sensitive and will undergo abrupt change in solubility in response to increases in environmental temperature at LCST which is governed by the balance of hydrophilic and hydrophobic moieties on the polymer chains. At the LCST, phase separation occurred because the balance of hydrophilic and hydrophobic moieties on the polymer chain was broken which resulted in a more hydrophobic structure of the polymer. Thermoreversible chitosan/HPMC composite hydrogels were fabricated, and LCST was increased with the increment of chitosan proportion in the composite hydrogels. For HPMC gelation, hydrophobic associations among the macromolecules possessing the methoxy group are the main mechanism. As temperature increases, hydrated and simply entangled polymer chains gradually lose their water of hydration with hydrophobic associations and form the hydrogel network. By adding chitosan, the concentration of HPMC was decreased, and hydrogen bond between the OH groups of HPMC and NH_2 groups of chitosan enhanced the interactions of two macromolecules. The ionization of the amino groups extended the distance between the chitosan molecules through cationic repulsion and favored the osmotic flow of the water into the network. Therefore, the hydrophilicity of the composite was enhanced resulting in the increased LCST [112]. The composite hydrogels displayed excellent thermal stability and good mechanical properties [113]. The composite hydrogels physically crosslinked by hydrogen bonding of carboxymethyl chitosan with HEC and MC were prepared for controlled drug release system. Better interaction is demonstrated in HEC composite hydrogels than that in MC composite hydrogels, owing to stronger intermolecular hydrogen bonding [114]. Polyol was also introduced into chitosan/HEC composite hydrogels to strengthen the hydrophobic interactions resulting in the incorporation of hydrophobic network into the hydrophilic network via IPN. The hydrophobic microenvironment can not only limit the swelling degree of the composite hydrogels but also act as reservoir of the drug [115]. The pH-responsive composite hydrogels slowed down the drug release rate by the moieties formed by hydrophobic network which was a promising approach to cover up the drawbacks of drug burst-release kinetics from the hydrogels [116]. The gelation temperature of CS-SO_3/MC/CMC was around body temperature which made it a good candidate for injectable thermosensitive hydrogels for postoperation anti-adhesion [32]. Chitosan/cellulose composite hydrogels can also be fabricated through the different solubilities of the macromolecules in various solvents. Both cellulose and chitosan can be dissolved in ionic liquid and coagulated to composite hydrogels by adding certain antisolvents such as water and ethanol. By this method, the lipase could be entrapped into chitosan/cellulose composite hydrogels with higher immobilization yields than cellulose hydrogels [117]. Chitosan/cellulose composite hydrogels also exhibited good cell compatibility and non-cytotoxicity. Magnetic hybrid hydrogels were obtained by coating cellulose and chitosan in ionic liquid on the surface of Fe_3O_4 which revealed high adsorption capacities for different heavy metal ions [118].

The amino groups of chitosan can be ionized in acid conditions to make it positively charged and form the composite hydrogels with negative-charged

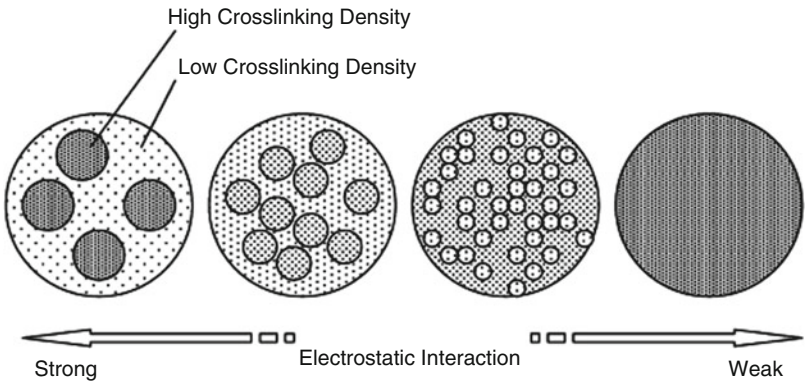

Fig. 5 Scheme representing heterogeneity of the chitosan/carrageenan/NaCMC composite hydrogels [120]

cellulose derivatives such as CMC via electrostatic interaction. Chitosan/CMC composite hydrogels showed pH-responsive swelling behavior. In acidic solution, amino groups of chitosan were protonized to NH^{3+} groups which coagulated with COO^{-} to form the condensed network, whereas in alkaline solution, the amino groups were neutralized, and electrostatic linkages between the two functional groups disappeared which resulted in the swelling of the hydrogels by the electrostatic repulsion between carboxyl groups. In vitro evaluations of capsaicin from chitosan/CMC composite hydrogels showed the reduced flux of capsaicin compared to the single-component hydrogels [119]. Chitosan/CMC/carrageenan ternary composite hydrogels were prepared by ionic crosslinking between NH^{3+} of chitosan with COO^{-} of CMC and SO_3^{-} of carrageenan. Both pH and addition of salt influenced the degree of swelling by changing the crosslinking density and/or the homogeneity of the network. As shown in Fig. 5, the composite hydrogels have the phase-separated structure, which is changed by the electrostatic interaction among three kinds of polyelectrolytes. The homogeneity of the composite hydrogels strongly depended on the composition of carrageenan/CMC and the salt concentration. When the chitosan or salt concentration was low, highly crosslinked part appeared in a relatively low crosslinked network. Increasing the chitosan or salt concentration, the difference in the crosslinking density in the homogeneous composite hydrogels would be small [120]. Chitosan/CMC composite hydrogels with core-shell structure were obtained by ionic crosslinking CMC with the Zr tetravalent metal ions firstly and further complexing with chitosan for the potential applications in bone tissue engineering [121].

3.1.2 Alginate

Alginate, a water-soluble polysaccharide composed of D-mannuronic and L-guluronic acid residues, is an abundantly available biopolymer extensively used for hydrogels, and the ionotropic gelation of alginate can be achieved with several cations. Alkaline earth metals, transition metals, and certain post-transition metals

are normally applied to form alginate hydrogels. Most of alginate/cellulose composite hydrogels were fabricated by utilization of the gelation of alginate with calcium ions, and cellulose was incorporated by dispersing in the composite hydrogels without taking part in forming the network. Water-soluble CMC is feasible to be mixed with alginate and crosslinked by Ca^{2+} to form alginate/cellulose composite hydrogels in order to remove some heavy metal ions such as Zn(II) [122], Chromium (VI) [123], and Hg(II) [124]. Both alginate and CMC are anionic in nature due to the presence of negatively charged carboxyl groups at pH $>$ 5. These negative charges allow the polymers to shrink in the acidic pH and to swell when they are exposed to neutral or basic pH. Therefore, alginate/CMC composite hydrogels prepared by the ionic gelation are good candidates of the drug delivery [125]. The crosslinking rate for trivalent ions was faster than that of divalent ions due to their higher valency; the Al^{3+} crosslinked alginate/MC composite hydrogels improved not only the drug encapsulation efficiency but also drug release in alkaline media [126]. Addition of CMC to alginate gel significantly improved the yield of lactase immobilization and the activity of the fixed enzyme [127]. CMC and its grafted copolymer were also incorporated into the alginate hydrogels by ionic crosslinking at the presence of inorganics to form the ternary composite hydrogels [128, 129].

Recently, alginate/bacteria cellulose (BC) composite hydrogels are gaining more and more attentions as scaffolds for tissue engineering by combining beneficial properties of both BC and alginate. BC has advantages in terms of biocompatibility, nontoxicity, high mechanical strength, high swelling ability, and high stability to pH variations. Alginate can provide mechanical integrity in tissue engineering applications for its hydrogel properties. Several therapeutic agents, including antibiotics, enzymes, growth factors, and DNA, have already been successfully incorporated in alginate hydrogels in order to maintain high biological activity [130]. Normally, the BC pellicles were crushed to form BC slurry and mixed with the alginate solution, then crosslinked by Ca^{2+} to obtain the composite hydrogels for scaffold. The compression strength and chemical stability of the alginate/BC composites were increased compared with the alginate hydrogels [131]; cell proliferation and migration on the surface of the scaffolds were promoted as well [130, 132]. Silver sulfadiazine particles, topical antibacterial agents, were embedded into the alginate/BC composite hydrogels to render the enhanced antibacterial property for utility as potential wound dressings [133]. Multi-walled carbon nanotube was incorporated into alginate/BC composite hydrogels to get a pH and electric field dual-stimulus responsive drug delivery system [134]. Alginate/BC composite hydrogels were also good immobilization carriers of lipase [135] and yeast [136]. In application in lipase immobilization, a novel in situ method was employed. Alginate solution was mixed with *G. xylinus* suspension firstly, and the resulting mixture was then added into $BaCl_2$ solution to gain the hydrogels. *G. xylinus* entrapped in the hydrogels successfully produced BC with a narrow distribution of fiber diameters. The prepared alginate/BC nanocomposite hydrogel beads showed consistent sizes and regular spherical shapes [135].

Alginate/cellulose composite hydrogels can be fabricated by ionic crosslinking by some trivalent cations with both macromolecules taking part in the formation of

network. Trivalent cations such as Fe^{3+} and Al^{3+} can induce the gelation of alginate; meanwhile, CMC can produce hydrogels by coordinating with these trivalent cations [137] due to numerous carboxyls and hydroxyls in the molecular chains. The trivalent iron can be a more suitable crossliking agent for alginate/CMC composite hydrogels than divalent metal ions in drug delivery system due to the faster crossliking rate which can result in the higher load capacity and sustained release [128, 138]. Protein, drugs, and some bioactive compounds can be encapsulated into the composite hydrogels and controlled released from them. Albumin was embedded into the Fe^{3+}-crosslinked alginate/CMC composite hydrogels, encapsulation efficiency was higher, and protein release was reduced in the gastric environment because of the pH sensitivity, which demonstrated that the alginate/CMC composite hydrogels presented a promising protein therapeutic carrier for the oral delivery [139]. The composite hydrogels also exhibited pH sensitive for delivering metformin hydrochloride (MH); the swelling degree and in vitro release profiles were higher by two orders at gastric conditions compared to an acidic environment [140]. Hesperidin-loaded efficiency in the alginate/CMC composite hydrogels was high, and in vitro release of hesperidin was prolonged. The composite hydrogels exhibited the ability to protect the encapsulated flavonoid glycoside during its passage through the simulated gastric environment, while under the simulated intestinal conditions, the transportation systems exhibited a pH-triggered release behavior [141]. The alginate/CMC composite hydrogels are also good absorbents to remove lead ions by physical, chemical, and electrostatic adsorptions [142].

Besides the ionic crosslinking, alginate and cellulose can be chemically crosslinked via some crosslinking agents to form the IPN composite hydrogels. There are numerous hydroxyl groups in both alginate and cellulose macromolecular chains; aldehyde groups of GA can form ether linkage with hydroxyl groups of alginate and cellulose as a result of the crosslinking reaction. Alginate/CMC composite hydrogels were prepared by crosslinking with GA and used for the delivery of carbaryl with higher entrapment efficiency. By increasing of exposure to GA or concentrations of GA, the crosslink density of the composite hydrogel matrix was changed to more compact network with increase in crosslink density resulting in reduced free volume and difficult diffusion of the carbaryl molecules [143]. AM was grafted onto HEC by free-radical polymerization and blended with sodium alginate to prepare pH-sensitive IPN composite hydrogels using GA as a crosslinking agent (Fig. 6). The covalent crosslinking leads to reduced swelling and introduces specific properties such as structural strength along with thermal and mechanical stability. In vitro release of diclofenac sodium was decreased with increasing GA content in the matrix due to the formation of a more tightly crosslinked rigid network structure [144]. ECH was also used as a crosslinker to react with the hydroxyl groups of cellulose and alginate chains through nucleophilic attack of the alcoholate anion, whereas a new epoxide formed by chloride displacement (Fig. 7). The combination of cellulose containing semi-stiff chain and alginate containing carboxyl groups created macroporous structure in the crosslinking hydrogels where cellulose contributed to support the pore wall and alginate acted as an expander of the pore size [145].

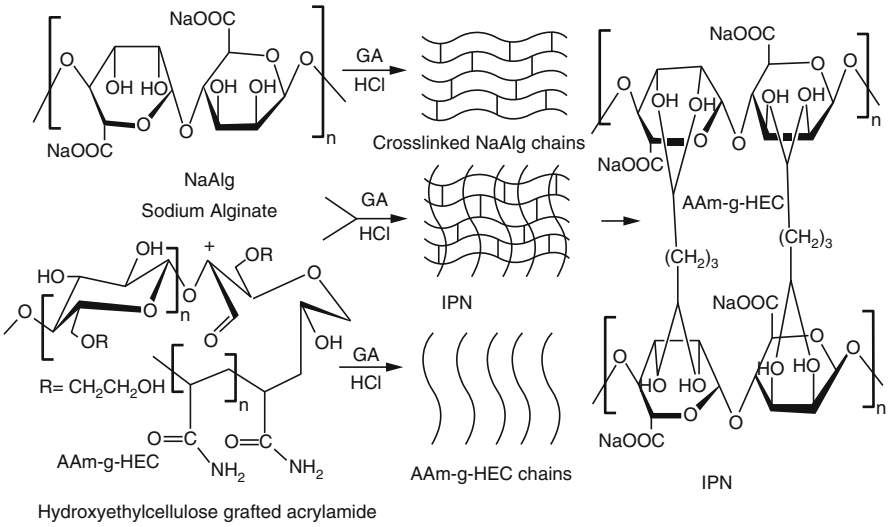

Fig. 6 Schematic representation of synthesis of IPN [144]

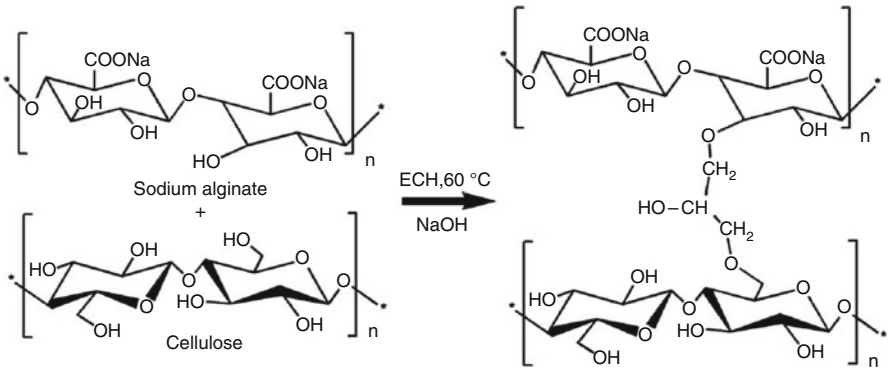

Fig. 7 Proposed mechanism for crosslinking reaction of cellulose and alginate with ECH [145]

3.1.3 Starch

Starch is an abundant renewable resource with low cost and broad-ranged capability in food and nonfood products. Starch granules have a semicrystalline structure, mostly composed of two different polysaccharides, amylose and amylopectin, with complicated internal structure. Starch/cellulose composite hydrogels can be prepared in chemical and physical crosslink of the network as well as with high-energy irradiation. Injectable adhesive hydrogels composed of starch and CMC were developed. Firstly, CMC was modified with tyramine to introduce crosslinking site, then the in situ hydrogel was prepared by an enzyme-mediated reaction of tyramine-immobilized CMC with horseradish peroxidase (HRP) and hydrogen peroxide (H_2O_2). Starch was added to the hydrogel solution to be incorporated in the cellulose

network as semi-IPN composite hydrogels. Starch can improve adhesiveness to the wound area and accelerate biodegradation of the hydrogels as injectable in situ anti-adhesive agents [146]. Starch/CMC/SiO_2 composite hydrogels were fabricated using aluminum sulfate octadecahydrate as an ionic crosslinker which increased the water restoration capability of agricultural soil [147]. Starch-g-PAA/NC composite hydrogels were obtained by in situ copolymerization of AA onto starch and crosslink with MBA (Fig. 8). The large amounts of active -OH groups on the surface of NC can take part in the polymerization reaction as well as the construction of 3D polymer network [148, 149]. Composite hydrogels were prepared with cellulose from tea residue [150] or pineapple peel [151] in ionic liquid, followed by incorporating soluble starch by mixing the cellulose hydrogel with starch. Addition of soluble starch exhibited good cell compatibility and non-cytotoxicity to the composite hydrogels. The composite hydrogels from HPMC and starch demonstrated the typical behavior of "filled" composite systems having poor adhesion between the surface of the elastic starch "filler" and the continuous HPMC phase [152].

High-energy irradiation technique is becoming an important approach in the crosslinking of polymers as it can efficiently replace the chemical crosslinking agents and produce hydrogels with high purity that do not need the removal of hazardous chemical crosslinkers. It allows the chemical crosslinking without the use of crosslinking agents which provides a convenient approach to crosslink polysaccharide at high concentrated aqueous solution mainly due to the mobility of side chains [153–155]. Side-chain radicals were formed mostly via indirect effects, by the abstraction of H atoms in the intermediate products of water radiolysis. Electron beam irradiation (EB) was used to prepare composite hydrogels from aqueous solutions of plasticized starch (PLST), cellulose acetate (CA), and CMC. A semi-IPN structure could be formed in which the network was mainly formed by crosslinked CMC and CA with PLST physically included [156]. Carboxymethyl sago pulp (CMSP)/carboxymethyl sago starch (CMSS) hydrogel was also synthesized by electron beam irradiation to produce the composite hydrogels with sustained release of drugs. The radicals on CMSP and CMSS chains can combine and form the intermolecular crosslinking between the molecular chains [157]. Gamma irradiation was also applied to prepare starch/CMC composite hydrogels as superabsorbent gels, in which the starch granules also participated in the

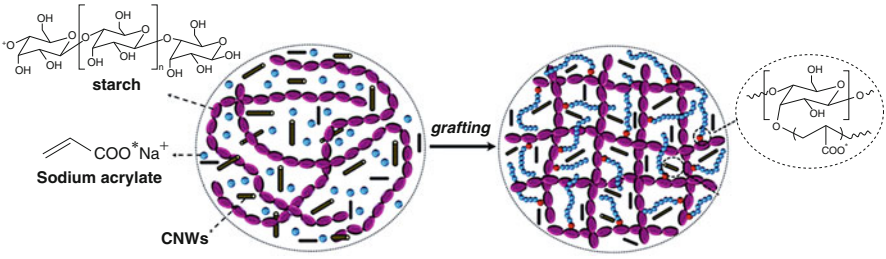

Fig. 8 Illustrative scheme for the structure of starch-g-poly(sodium acrylate)/CNWs composite hydrogels. Reproduced from [149]

crosslinking process resulting in the improved gelation. CMC chains reacted with the granule surface through the recombination of the radicals, and the reaction was not hindered by electrostatic repulsion during the crosslink formation between two CMC chains. The partial replacement of CMC with starch improved the gel fraction; however, very high starch content had a negative impact on the gelation [158].

3.1.4 β-CD

β-CD is a type of cyclic molecule composed of seven glucose units and derived from starch. β-CD possesses internal relatively hydrophobic cavity and exterior hydrophilic structure. These special structures make β-CD easy to form molecular complexes via interaction with other polymer network by virtue of intermolecular force. There are abundant hydroxyl groups in β-CD molecular; it is feasible to chemically crosslink β-CD and cellulose via some crosslinkers to obtain β-CD/cellulose composite hydrogels. Water-soluble CMC was crosslinked with β-CD via ECH, and the graft reaction involved usually nucleophilic substituent in cellulose. Meanwhile, β-CD of the heptatomic ring chain can attack the epoxy group of ECH and is then converted to a monoether of chloropropanediol [159]. Due to substitute and rearrangement of chloride, β-CD and CMC were linked together, and the network structure was constructed (Fig. 9). The prepared composite hydrogels were sensitive to changes of pH, temperature, and ionic strength [160]. NaOH/urea aqueous solution has been found to be a good solvent for cellulose; β-CD/cellulose composite hydrogels could also be synthesized in NaOH/urea aqueous solutions by crosslinking with ECH. Swelling degree of the composite hydrogels decreased with an increase of the β-CD content. The drug-loading capacity of the composite hydrogels was preferred to the hydrophobic drug due to the formation of complexation; however, only the molecules which can form a stronger inclusion complex with β-CD [161] can promote the release of the drug. The composite hydrogels-adsorbed aniline blue also caused enhanced fluorescence intensity with the potential application as a biological stain [162].

Citric acid (CA) has gained recognition as a nontoxic crosslinking agent for grafting β-CD onto cellulose, and anhydride formation of CA facilitated the ester crosslinks between cellulose and β-CD (Fig. 10). β-CD-grafted HPMC [163] and β-CD-grafted

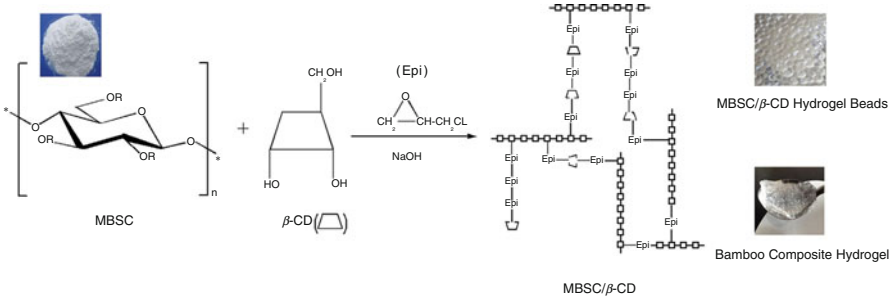

Fig. 9 Synthesis of the β-CD/cellulose composite hydrogels [159]

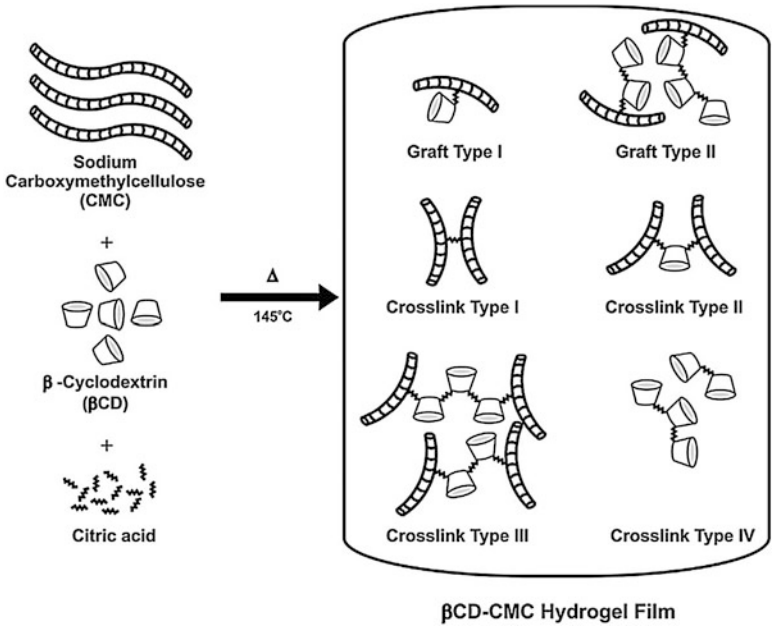

Fig. 10 Schematic representation of the formation of β-CD-CMC hydrogel film [164]

CMC [164] composite hydrogels were obtained with CA, and the controlled delivery of drugs with poor solubility of those composite hydrogels was investigated. The active β-CD content, carboxyl content, and swellability showed major contributions toward improvement of drug loading and retardance of drug release [163].

Hydroxypropyl-β-cyclodextrin (HPβCD) was crosslinked with HPMC via EGDE under mild conditions to prepare β-CD/cellulose composite hydrogels [165]. 1,4-butanediol diglycidyl ether (BDGE) was used as crosslinker to form β-CD/HPMC composite hydrogels which were conjugated with antimicrobial gallic acid to prevent wound infection [166]. β-CD and CMC were graft polymerized with AA, in the presence of MBA as a crosslinker to prepare β-CD/CMC-g-PAA composite hydrogels. The pH-sensitive composite hydrogels were conferred good mechanical properties with improved drug loading and release capability for the antiviral drug acyclovir [18].

β-CD can be incorporated into β-CD/cellulose composite hydrogels by non-covalent interactions as well. Hydrophobic cavities of β-CD can act as moieties capable of generating physical crosslinks, by making inclusion complexes with hydrophobically modified polymers or with amphiphilic polymers with hydrophobic chains, which combined to form host-guest complexes networks. β-CD can also be modified by some anionic or cationic groups to make it charged and form the composite hydrogels with opposite charged polymers via electrostatic interaction.

Cellulose can be dissolved in the mixed solvent of tetrabutylammonium hydroxide (TBAH) and Dimethyl sulfoxide (DMSO) because TBAH is capable to dissolve cellulose at the molecular level with effectively repulsive cellulose-cellulose

interactions. Stiff composite hydrogels were formed when adding β-CD to the cellulose dopes because the formation of 1:1 β-CD:TBA+ host-guest complex [167] destabilized the cellulose solution state and triggered the composite hydrogels formation [168]. β-CD and ferrocene (Fc) were grafted onto cellulose individually to obtain β-CD-cellulose and Fc-cellulose; firstly, the composite hydrogels can be prepared by mixing two solutions by formation of inclusion complexes. The ferrocene forms of the inclusion complexes with β-CD effectively, whereas the oxidized ferrocene is basically impossible. Therefore, the host-guest interaction between the metal ferrocene with β-CD can also be a reversible regulation by oxidation and reduction of the ferrocene which resulted in the controlled sol-gel transition [169]. The hydrophobic lauryl side chains were grafted onto HEC firstly and mixed with water-soluble β-CD polymers. The cavities of β-CD polymers can provide hydrophobic binding sites with C12 side chains to obtain self-assembled composite hydrogels based on the host-guest interaction, and the residual cavities of composite hydrogels can load drugs (Fig. 11) [170]. β-CD-grafted NC was accomplished using ECH as a coupling agent and pluronic polymers were introduced on the surface of NC by means of inclusion interaction between β-CD and hydrophobic segment of the polymers to obtain supramolecular hydrogels [171].

Chitosan/HEC hydrogels were prepared by crosslinking firstly, the negative sulfonatedbutyl (SEB) β-CD (SEB-β-CD) was loaded into the hydrogels simply by immersing the hydrogels into the SEB-β-CD solution. The electrostatic interaction of cationic chitosan and anionic SEB-β-CD was the main driving force to immobilize the β-CD into the hydrogels. Moreover, the encaged SEB-β-CD can be controlled and released from the composite hydrogels with ion-exchange method by immersing it in electrolyte solution readily [94]. In addition, hydroxypropyl-β-CD (HP-β-CD) was immobilized into HEC [172], HPC [173], and HPMC [174] hydrogels at the same time of the crosslinking of cellulose derivatives.

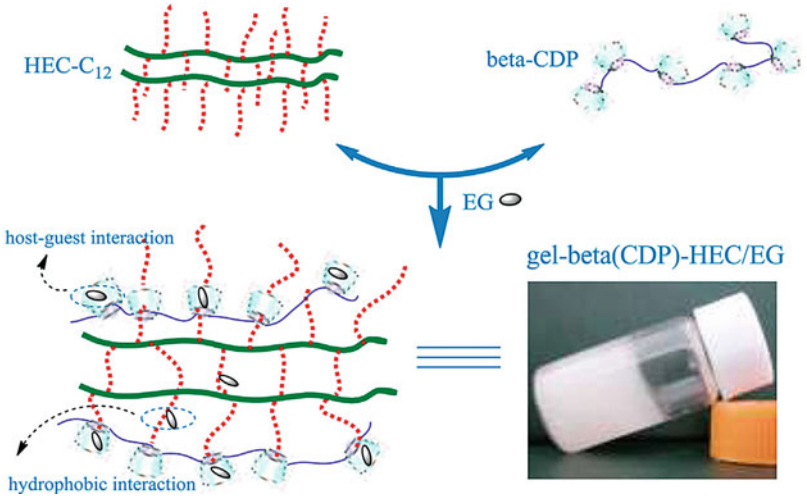

Fig. 11 Scheme of the formation of self-assembled hydrogels and its drug-loading pattern [170]

3.2 Extracellular Matrix

The extracellular matrix (ECM) is the noncellular component presenting within all tissues and organs that not only provides essential physical scaffolding for the cellular constituents but also initiates crucial biochemical and biomechanical cues [175, 176]. The composite hydrogels-combined cellulose and ECM are very promising scaffolds for the tissue repair and regeneration, especially for the injectable self-healing hydrogels with the dynamic interactions. Collagen as a key ECM component for promoting cell cultivation is most widely used to fabricate the composite hydrogels, especially for bone reparation because of its weak antigenicity, excellent biocompatibility, and unique fibril-forming properties. Collagen is a kind of protein forming a characteristic triple helix of three polypeptide chains, and all members of the collagen family form these supramolecular structures in the extracellular matrix although their size, function, and tissue distribution vary considerably [177].

Dialdehyde cellulose is an attractive cellulose derivative because it can react with amino functional groups in collagen by the formation of Schiff base-type compounds [178, 179]. Regenerated cellulose hydrogel was obtained firstly and oxidized by periodate oxidation to obtain 2,3-dialdehyde cellulose (DARC) which presented a porous structure with tangled fibrils and interconnected networks. This unique structure was attributed to the phase separation of the cellulose solution during the regeneration process, where solvent-rich regions contributed to the formation of pores. Collagen was immobilized on cellulose via the Schiff base reaction between -NH_2 in collagen and -CHO in DARC (Fig. 12). The self-crosslinked composite hydrogels showed great potential for use as a tissue engineering scaffold due to its high strength, malleability in situ, good equilibrium-swelling ratio, air permeability, and biocompatibility [180]. DCMC [181] with substantial degradation in periodate oxidization induced the crosslinking of collagen to macroporous structure [182].

The cellulose hydrogels were prepared from cellulose solution dissolved in LiOH/urea aqueous system by crosslinking with ECH and then thermal crosslinked collagen by neutralizing the collagen solution to obtain collagen/cellulose composite hydrogels. The composite hydrogels integrated microfluidics with well-controlled pore size, good mechanical durability, cytocompatibility in cell culture, and excellent dimensional stability [183]. The amino groups in collagen provide Cu(II) binding

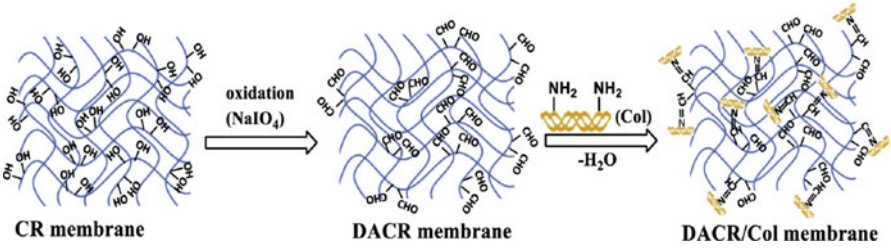

Fig. 12 The schematic diagram of the preparation of DARC/Collagen (DACR/Col) composite film [180]

sites through their chelating performance [184]. Collagen/cellulose hydrogel beads reconstituted from ionic liquid showed high Cu(II) adsorption capacity for removal of it from wastewater [185].

BC displays many unique properties including high water uptake capacity and an ultrafine nanofibril network structure which are essential for scaffolds in tissue engineering. To improve the biocompatibility and cell affinity of BC as wound dressing material, BC can be modified through the incorporation of collagen, and the collagen/BC composite hydrogels are very promising materials in skin tissue engineering. Collagen/BC composite hydrogels can be prepared by simply immersing wet BC pellicle into collagen solution followed by a freeze-drying process. The collagen molecules were not only coated on the BC fibrils surface but also penetrated inside BC, and hydrogen bond interactions were thus formed between BC and collagen [186]. According to the in vivo test and macroscopic evaluation, collagen/BC composite hydrogels showed better reparation ability of wounds and promoted statistically significant differences of tissue repair between treatments after surgery [187]. BC formed semi-penetrate hydrogels with alginate and immobilized collagen to ternary composite hydrogels which supported the growth of human skin fibroblast as deliver vehicles for therapeutic compounds during wound healing [188]. In order to improve thermal and mechanical properties of collagen/BC composite hydrogels, both GA and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride were used as crosslinkers to form the chemical bonds between collagen and BC [189].

3.3 Nanocellulose/Natural Macromolecules

NC can also be incorporated into natural macromolecules hydrogels such as chitosan, alginate, and gelatin which targeted biological or biomedical applications. GA was used as a crosslinker to chitosan because of its high reactivity toward the amine groups, and NC was incorporated into the network to improve mechanical properties and pH sensitivity of the chitosan/NC composite hydrogels [190, 191]. Carboxymethylated chitosan/NC aerogel for dye removal was prepared through Schiff base reaction. NC, bearing aldehyde and carboxylic acid groups, facilitated the crosslinking with chitosan through imine bond formation while providing negatively charged functional groups, and chitosan was modified to accommodate carboxylic acid [192]. Chitosan/NC sponge was prepared by lyophilization to be used as a new absorbable hemostat [193]. The carboxyl groups of NC and amino groups of chitosn were linked with peptide bonds forming stable hydrogel network [194]. Chitosan-g-PAA/NC composite hydrogels obtained by in situ polymerization showed responsive behavior in relation to pH and the salt solution [195]. Chitosan/NC/xanthan [196] and chitosan/BC/MMT [197] ternary composite hydrogels were also fabricated by lyophilization. Chitosan/BC composite hydrogels were prepared by co-dissolution of BC and chitosan in 1-Ethyl-3-methylimidazolium acetate ([Emim][Ac]) and reconstitution with water [198] or in situ method during biosynthesis which showed better effect on cell growth, cell proliferation, and biocompatibility [199].

For alginate/NC composite hydrogels, NC normally acts as reinforcement filler embedded in the alginate hydrogels crosslinked by metal ions. The alginate/NC composite hydrogels are effective absorbents to organic dyes [200], and the reusable composite hydrogels showed more than 97% dye removal efficiency after five successive adsorption-desorption cycles [201]. Alginate/BC hydrogel membrane was also used for separation of ethanol-water mixtures [202]. NC was firstly biofunctionalized by the covalent coupling of an enhanced avidin protein and used to fabricate 3D-printable bioactivated alginate/NC composite hydrogels [203]. IPN hydrogels based on NC in a matrix of alginate/gelatin were prepared via freeze drying and stabilized using $CaCl_2$ and genipin which were potential in load-bearing biomedical applications such as cartilage replacement (Fig. 13) [204]. Double-membrane hydrogels from cationic NC and anionic alginate involved with an internal membrane consolidate by electrostatic interactions. The composite hydrogels with double-layer structures can realize the complexing drugs release with the first quick release of one drug and the successively slow release of another drug [205].

NC was employed to reinforce the cellulose and its derivative hydrogels such as CMC/HEC [206] and MC [207]. Injectable hydrogels based on CMC and dextran, reinforced with rigid rodlike NC as simple fillers and aldehyde-functionalized NC as chemical crosslinkers, were prepared with potential applications such as drug delivery vehicles or tissue engineering matrices [208]. Composite hydrogels based on CMC-g-P(AA-co-AM) and carboxylate NC were prepared by in situ graft polymerization in the presence of NC, and results showed that the composite hydrogels comprised a crosslinking structure of NC and CMC with side chains carrying AA and AM [209]. Gelatin [210, 211], collagen [212–215], and starch [148, 149, 216] were also applied to fabricate the composite hydrogels with NC.

4 Inorganics/Cellulose Composite Hydrogels

4.1 Inorganic Minerals

Layered silicate, such as MMT, can form the microcomposite (Fig. 14a) and nanocomposite (Fig. 14b, c) hydrogels with polymers. The silicate can dispersed in the hydrogel matrix in nanoscale with two main structures: (1) intercalated (Fig. 14b), the polymer chains are inserted into the interlayer spacing of the stacking silicate platelets and (2) exfoliated (Fig. 14c), the individual layers are partitioned and dispersed in the polymer matrix. The exfoliated structure is more effective to improve the properties of the composite hydrogels for its greater phase homogeneity. Moreover, the polymer can act as a crosslinking agent by reacting with the groups on the surface of the inorganic plate. As shown in the Fig. 14d, the silicate platelets provide high surface area for multiple sites of crosslinking; meanwhile the polymer chains are flexible and can adopt random conformations for the long distances between the clay sheets which provide the cushion when the composite hydrogels are stretched or compressed. The performance of the clay composite hydrogels is

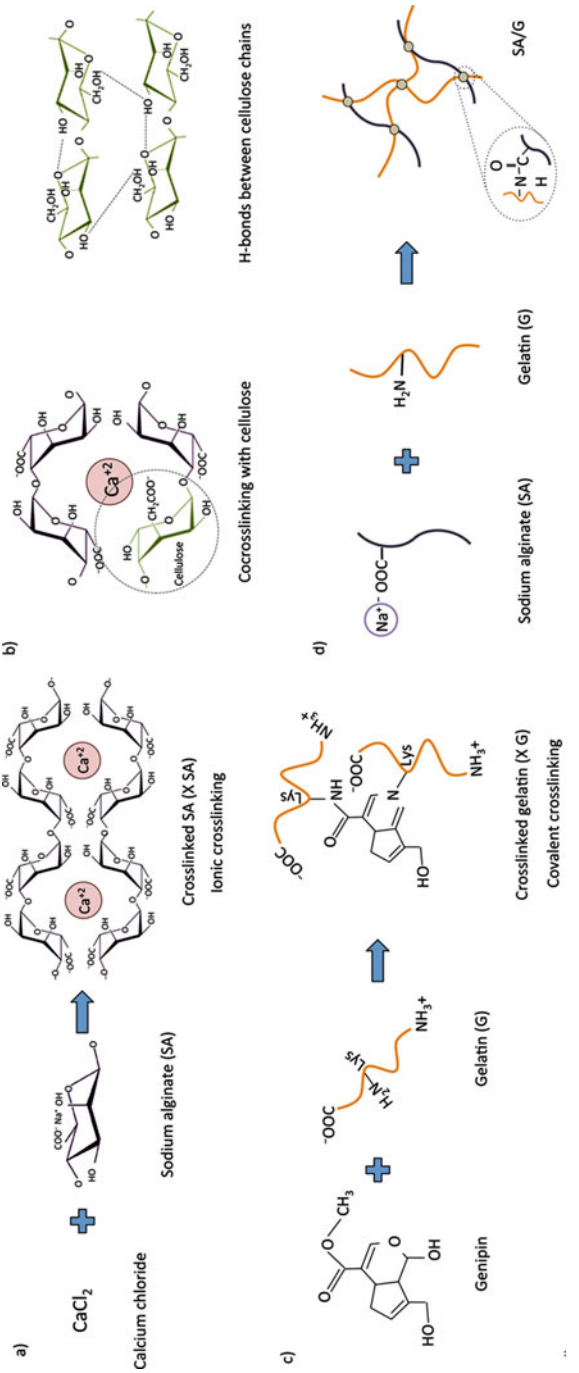

Fig. 13 Mechanisms of crosslinking reactions of (**a**) alginate/$CaCl_2$, (**b**) alginate/NC, (**c**) genipin/gelatin, and (**d**) alginate/gelatin. (Reproduced from [204])

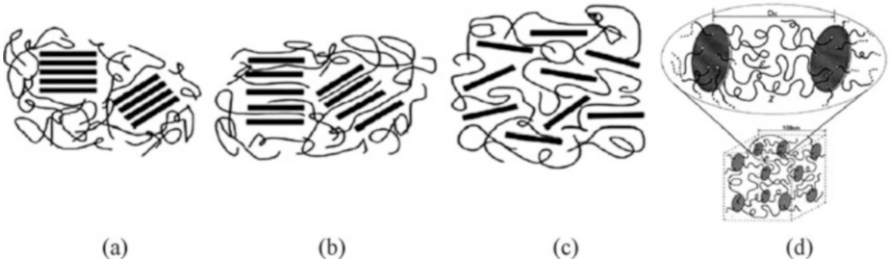

Fig. 14 Types of layered particle reinforced composites. (Reproduced from [217, 218])

largely influenced by the clay content and homogeneous dispersion in the matrix [217]. Compared to the monocomponent hydrogels, composite hydrogels have the combined properties of high mechanical strengths, elongations at break, and high rates of swelling/deswelling.

Vinyl monomers such as AA and AM can be in situ polymerized and grafted onto the chains of cellulose derivatives in the presence of the layered silicate to prepare the composite hydrogels. The obtained superabsorbents revealed that the inorganic particles could be incorporated into the hydrogels matrix by reacting through the active groups on the surface. Silanol groups on the attapulgite (APT) [219] and hydroxyl groups on the MMT [220] make them facilitate to participate in the graft polymerization of CMC side chain of vinyl monomers. The remarkable pH sensitivity swelling behavior of the composite hydrogels was observed. Compared to the effects of cellulose derivates on swelling properties of the composite hydrogels, equilibrium water absorbency and the swelling rate in distilled water and saline solution are always in the order CMC > HPMC > MC > HEC. It was revealed that the influence of functional groups on swelling properties was great and the swelling properties of composite hydrogels were related to the hydrophilicity and the rigidity of functional groups [221]. Carboxyl group is an ion hydrophilic group which can be ionized; therefore, the polymeric network tends to swell, and the space for absorbing and holding water increases due to electrostatic repulsion. Moreover, the higher osmotic swelling pressure and chain relaxation process of CMC make it possess the higher swelling rate than other cellulose derivatives. Therefore, CMC is suitable to fabricate the inorganics/cellulose composite hydrogels for superabsorbent.

MMT is one of the most widely used layered silicates because its lamellar elements display high in-plane strength, stiffness, and high aspect ratio, which are beneficail to the properties of the composite hydrogels such as swelling ability, mechanical strength, and thermal stability. It has a 2:1 layer structure consisting of an octahedral alumina sheet sandwiched between two opposing tetrahedral silica sheets. The bonding between two silica sheets is very weak, which permits the water, exchangeable ions, and polymer chains to enter, and this leads to the development of nanocomposite hydrogels and their swelling capacity. The reactive hydroxyl groups and exchangeable cations on the surface of MMT can also make it act as a crosslinking agent between cellulose chains [220] and in situ intercalative polymerization [222, 223].

Cellulose-g-P(AA-co-AM-co-AMPS)/MMT composite hydrogels for superabsorbent were synthesized by using potassium persulfate as a free-radical initiator, in the presence of MBA as a crosslinking agent. The composite hydrogels comprised a crosslink structure of MMT and CMC with side chains that carried carboxylate, carboxamide, and sulfate [220]. CMC, MMT, and 2-acrylamido-2-methyl-1-propanesulfonic acid (AMPS) could be incorporated into AM hydrogels during free-radical solution polymerization; meanwhile the multifunctional crosslinker such as poly(ethylene glycol)diacrylate was used at the polymerization process to fabricate the highly swollen composite hydrogels [224]. Cellulose-g-PAA/MMT nanocomposite hydrogels were proved to be effective in controlled release of macro- and micronutrients; furthermore, a hydrolysis treatment improved their physicochemical properties. The presence of MMT not only remarkably enhanced their capacities of loading nutrient solutions but also acted as an effective barrier to control and retard the release of nutrients to the medium as well as played an important role in reducing production costs [225]. CMC-g-poly(NIPAM-co-AA)/MMT hydrogels were prepared by graft copolymerization of NIPAM and AA onto CMC in MMT/water suspension media, which were thermoresponsive and pH-sensitive hydrogels for removal of heavy metal ions from aqueous solutions [226]. MC was also used to prepare the nanocomposite hydrogels with PAM and MMT to slowly release of fertilizers [33]. Cellulose/MMT composite hydrogels were fabricated by chemical crosslinking cellulose and CMC with ECH in the presence of MMT nanosheets. MMT was first modified in order to make it take part in the formation of hydrogel network by reacting with cellulose. In this case, cellulose chains entered the galleries of MMT, and intercalated nanocomposite hydrogels were fabricated for highly efficient removal of dye in water [227].

Bentonite is a type of clay mainly composed of the crystalline structure of MMT and other additional crystalline structures. Composite hydrogels were synthesized by the graft copolymerization reaction among cellulose, polymethacrylic acid (PMAA), and bentonite; the inorganic bentonite particles in the network acted as additional network points. The PMAA-g-cellulose/bentonite could be effectively used as an adsorbent for the removal of dyes from water and wastewater [228]. CA-crosslinked CMC/bentonite composite hydrogels were prepared to develop base triggered release formulations of thiamethoxam due to their high swelling sensitivity under the basic pH condition, low cost, and environment-benign nature. Bentonite was added in the composite hydrogels to improve the barrier properties of formulations with enhanced rheological properties [229]. A new composite matrix for the controlled release of herbicides was prepared by adding bentonite or its acid-activated form into CMC gel [230].

Halloysite nanotubes (HNTs) with similar chemical formula as kaolinite possess unique empty lumen tubular morphology with outer diameters of 50 nm and inner lumens of 20 nm and 200–1000 nm long. They are biocompatible and widely available in nature, which make them good candidates for application in biomedicine by protecting the drug from enzyme degradation and delivery of the drugs to enter the cell. HNTs can be easily incorporated via solution mixing for cellulose composite hydrogels. HNTs were mixed into cellulose NaOH/urea solution to prepare

composite hydrogels using ECH crosslinking at elevated temperature, and curcumin-loaded composite hydrogels showed a strong inhibition effect on the cancer cells and good cytocompatibility [231]. HNTs were firstly modified by the reaction of the external silanol groups with maleic anhydride and further reacted with adipic acid dihydrazide to introduce a hydrazine moiety on the clay surface. Functionalized HNTs were mixed with oxidized CMC to form biodegradable hydrazone bond to prepare the injectable composites hydrogels with potential applications in bone medication [232].

Similar to MMT, carclazyte is a layered aluminum silicate with exchangeable cations and reactive -OH groups on the surface. CMC-g-poly(AA-co-AM)/carclazyte composite hydrogels for superabsorbent were synthesized by graft polymerization of AA and AM onto CMC and the introduction of carclazyte. Additionally, ammonium persulfate (APS) and MBA were used as a free-radical initiator and a hydrophilic crosslinking agent, respectively [233]. Medicinal stone is a special igneous rock composed of silicic acid, alumina oxide, and more than 50 kinds of constant and trace elements. Vermiculite is a trioctahedral 2:1-layered silicate similar in texture to mica, and it is abundant and much cheaper in comparison with MMT [234]. Both medicinal stone and vermiculite can be incorporated with HEC-g-PAA to fabricate the composite hydrogels by the free-radical polymerization among HEC and AA which exhibited the enhanced swelling capability, swelling rate, excellent pH-responsive and good deswelling capability as potential water-manageable materials [46, 235].

4.2 Antimicrobial Nanoparticles

The synthesis of cellulose/nanoparticles hybrid composite hydrogels has attracted increasing attention especially for the nanoparticles (NPs) with special functions. Metallic NPs with inherent antimicrobial properties such as Ag, Zn, Au, and Cu are known to have broad-spectrum antimicrobial nature and pose minimum toxicity to humans. Particularly, nanosilver-based wound dressings have received approval for clinical applications, but dermal toxicity was reported [236]; therefore, the combination of hydrogels with silver NPs (AgNPs) is a better choice for the treatment of wounds [237]. There are free spaces within the cellulose hydrogels that could be utilized to incorporate NPs; meanwhile the incorporation of NPs into the hydrogel matrix reduces their agglomeration. Development of cellulose/NPs composite hydrogels is important to control growth of pathogenic microorganisms for the prevention of infectious diseases with good biocompatibility in the medical field. However, NPs have a tendency to aggregate to minimize their surface energy, which decreases their antimicrobial activity [238] and hinders the large-scale production with cost-effective dispersion methods. The methods of composite hydrogels preparation have a great influence on the structure and properties of the resulting composite hydrogels. For the preparation of cellulose/NP composite hydrogels, metals NP can be incorporated via two approaches: (1) ex situ, in which pre-synthesized NPs are incorporated into the cellulose hydrogel matrix and (2) in

situ, in which cellulose matrix acts as a nano-reactor for synthesizing NPs. The antimicrobial NPs must be integrated in isolated and well-dispersed primary NPs inside the cellulose matrix to obtain the homogeneous composite hydrogels with good mechanical strength and enhanced antimicrobial activity.

4.2.1 AgNPs

AgNPs, efficient antimicrobial agents with little toxicity, are utilized in clothing, medical devices, cosmetic and pharmaceutical goods. AgNPs constitute an important component in nano-enabled consumer products available in the market. They are the most desirable antimicrobial NPs to be incorporated into the cellulose hydrogels. The antimicrobial property of AgNPs is governed by their size, shape, aggregation state, and so on. It is widely accepted that smaller the size of AgNPs is more beneficial to the antimicrobial activity due to higher penetration rates. Although the truncated AgNPs appear to be higher antimicrobial efficiency than spherical AgNPs, spherical AgNPs are usually preferred over other shapes due to their ease in synthesis, controlling on particle size, handling, and recovery for use. Hydrogels can afford free spaces between the networks in the swollen stage that serve for nucleation and growth of NPs and act as nanoreactors or nanopots. The crosslink densities were proved to be important in controlling the size and shape of the AgNPs within the hydrogel networks which was a facile synthetic strategy for tuning AgNPs to the desirable morphology (Fig. 15) [239].

CMC [240, 241] and hydroxypropyl CMC [242] can be used as reducing and stabilizing agents for green preparation of AgNPs, the hydroxyl groups form coordination bonds with silver ions, and carboxylic groups have electrostatic interaction with Ag ions which facilitate the reduction of Ag ions by CMC. A two-step process was the most common mechanism for synthesis of AgNPs, i.e., single-atom formation and then polymerization of the atoms to a particle. Firstly, a portion of metal ions in a solution is reduced by the available reducing groups of the cellulose and its derivatives; the produced atoms act as nucleation centers and catalyze the reduction

Fig. 15 Hydrogel networks used as templates to synthesize of silver NPs [239]

of the other metal ions remaining in the bulk of solution. Subsequently, these formed atoms coalesce together to form metal clusters, and the ions attracted to the surfaces of these clusters are reduced further to aggregate to NPs. The formed particles are stabilized by a layer from the polymer matrix, thus preventing further coalescence of these NPs to larger particles [242, 243]. Synthesis procedures using microwave irradiation were also employed to accelerate the process. Microwave radiation of CMC and silver nitrates solution produced uniform AgNPs that were stable for 2 months at room temperature [244].

In situ: Cellulose and its derivatives can be chemically crosslinked into hydrogels, and AgNPs can further be incorporated into hydrogels matrix by in situ synthesis. CMC was converted to hydrogels using ECH as a cross linking agent. Two strategies were employed to obtain the CMC/AgNPs composite hydrogels: the first involved reaction of ECH with CMC in alkaline medium containing silver nitrate to synthesize AgNPs and form CMC networks simultaneously; the second entailed previous preparation of CMC hydrogel and reduction Ag^+ ions into AgNPs within the swollen hydrogels. Both of CMC/AgNPs composite hydrogels showed uniform distribution of NPs in the hydrogels matrix, and the composite hydrogels obtained by the first strategy exhibited high antibacterial activity against Gram-positive and Gram-negative bacteria [237]. Fumaric acid was also used as a crosslinker to prepare the CMC/AgNPs composite hydrogels with the first strategy to render cotton fabrics for antibacterial property with the potential applications in wound dressings [245]. With the second strategy, hydrogels with CMC, PVA, and the crosslinker EGDE were fabricated, and AgNPs were incorporated by using trisodium citrate as a reducing agent under microwave radiation. The hydrogel matrix mainly provides steric protection to the Ag^+ due to the polymeric network by direct bonding with these electron donor sites. The obtained composites hydrogels exhibited high antibacterial activity against urinary tract infection (UTI) pathogens [246]. CMC-poly (diallyldimethylammonium chloride) (DADMAC) hydrogels were fabricated by graft copolymerization of DADMAC onto CMC using APS as a free-radical initiator and MBA as a crosslinker. AgNPs or CuO NPs were incorporated into the hydrogels by immersing the CMC-poly(DADMAC) hydrogels into $AgNO_3$ solution or copper sulfate solution and reducing or oxidizing to NPs in situ. The prepared composite hydrogels can be used in different medical fields, i.e., drug delivery and wound dressing as well as wound healing [247]. Semi-IPN hydrogels based on crosslinked PAM through an optimized rapid redox solution polymerization with MBA in presence of CMC were synthesized, and silver ions were in situ reduced using *Azadirachta indica* (Neem) plant extract under atmospheric conditions. The obtained pH-responsive composite hydrogels were suitable to safely transfer the drug through the stomach with acidic pH and release it successfully in the basic environment of the colon [248]. AgNPs can be transformed into Ag_3PO_4 NPs by the reaction of Ag and HPO_4^{2-} to prepare Ag_3PO_4/cellulose composite hydrogels [249].

Layered double hydroxides (LDHs) which consist of brucite-like sheets containing both bivalent and trivalent cations were employed to prepare physically crosslinked CMC composite hydrogels by intercalating CMC into different LDHs. AgNPs/CMC-LDH composite hydrogels were prepared through in situ formation of AgNPs within

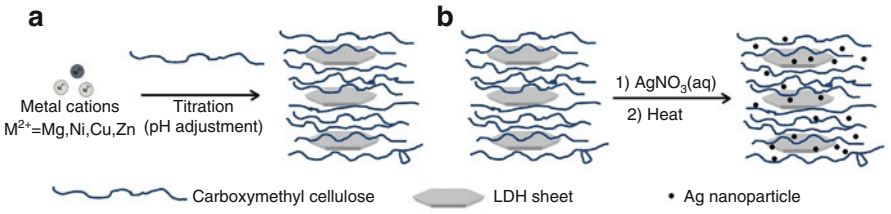

Fig. 16 The schematic representation of the formation of CMC-LDH hydrogels (**a**) and AgNPs/CMC-LDH composite hydrogels (**b**). (Reproduced from [251])

the CMC-LDHs hydrogels. Figure 16a illustrated the formation of CMC-LDH hydrogels through co-precipitation by dropping solution of mixed M^{2+}/Al^{3+} metal ions into alkali-CMC solution in order to precipitate LDH layers and intercalate CMC chains into LDHs. The electrostatic interaction between negative CMC and positive LDH sheets made LDHs act as inorganic crosslinkers in the composite hydrogels. Figure 16b represented the immobilization of AgNPs in the CMC-LDH hydrogels by in situ synthesis of AgNPs by the utilization of CMC as reducing and stabilizing agents. The silver ions are exchanged to the CMC-LDH networks firstly by anchoring through -COONa and -OH groups in CMC chains and then followed by reduction with the existing hydroxyl groups in CMC [31–33]. The LDH surface not only acts as a substrate to anchor and grow AgNPs but also is important in the stabilization of NPs through interactions between NPs and hydroxyl groups of the LDH surface [250]. AgNPs were well distributed within the AgNPs/CMC-LDHs composite hydrogels, and the hydrogels revealed a pH-dependent swelling behavior and good antibacterial activity to both Gram-negative and Gram-positive bacteria [251].

NC can also form the composite hydrogels with AgNPs by in situ reduction of Ag ions [252, 253]. The negatively charged surface carboxylate groups of TEMPO-oxidized NC provide high binding capability to Ag ions which triggers rapid gelation of the NC because transition metals are capable of resulting in carboxylate metal ion complex formation. Simultaneously, Ag^{+} was reduced slowly into AgNPs with prevalent hydroxyl groups on NC without additional reducing agents [252]. BC fibers are assembled by bundles of thinner cellulosic fibers with diameter sizes down to micro- and nanoscale. An extended network is observed via both intramolecular and intermolecular hydrogen bonds [254] enabling the production of sheets with high surface area and porosity. BC network has a very high affinity for water which results in hydrogel-like properties; therefore, BC hydrogel can embed the NPs to fabricate the composite hydrogels. GO-AgNPs/BC hydrogel microfibers were prepared with the microfluidic technology which exhibited a well-defined coaxial cable-like structure, with GO-AgNPs in the inner-core layer and BC hydrogel in the outer-shell layer. GO-AgNPs/BC hydrogel microfibers revealed efficient activity to sterilize both Gram-positive and Gram-negative bacterial strains with low cytotoxicity [255]. AgNPs/BC composite hydrogels could be obtained by UV light irradiation in situ with AgNPs photochemically deposited onto the BC gel network as well as chemically bonded to the cellulose fiber surfaces [256].

Ex situ: The super-macroporous polymer hydrogels based on HPC and PAM were obtained by UV irradiation of moderately frozen systems, using hydrogen peroxide as a source of radicals. H_2O_2 generated hydroxyl radicals during its photo-homolysis which reacted with the polymer molecules giving rise to macro-radicals. The crosslinking occurred by intermolecular recombination of two macro-radicals. AgNPs were immobilized in the channels of the gel by immersing a freeze-dried HPC cryogel in aqueous dispersion of AgNPs or incorporated into the polymer matrix by mixing of the AgNPs dispersion and HPC followed by freezing and subsequent crosslinking. The two types of composite hydrogels exhibited completely different releasing process of AgNPs; the gels containing AgNPs only in the channels could release them immediately by compression, while the gels with AgNPs embedded in the walls exhibited a slow release of Ag for months because AgNPs were physically entrapped within the dense polymer network. Thus, composite hydrogels with different release profiles could be obtained by different ex situ incorporation methods which were beneficial to controllable release of AgNPs [257]. Cellulose-based sponges were developed by freeze drying of regenerated cellulose gels and incorporated the prepared AgNPs by immersing the sponges into the AgNPs suspension. The composite sponges showed excellent antibacterial activity with prolonged release of AgNPs, high sorption of simulated wound fluids, and high water vapor transmission ability due to hydrophylicity of cellulose and porous structure, resulting in the cellulose-based sponges as promising wound dressing materials for fester and infected wounds [258]. AgNPs can also be coated with PEG, sodium dodecyl sulfate, and β-CD before loading into the cellulose hydrogels in order to improve the stability of the NPs and reduce the growth of the particles via trapping of seeds and steric repulsion [259].

4.2.2 ZnO NPs

ZnO NPs possess antibacterial activity to both Gram-positive and Gram-negative bacteria which may be related to the induction of oxidative stress due to generation of reactive oxygen species and the degradation of the membrane structure of the cell. They even have antibacterial activity against spores that are high-temperature-resistant and high-pressure-resistant [260]. Due to the lower cost, lack of color, and UV-blocking properties of ZnO NPs, they are used as alternatives to AgNPs to incorporate with cellulose hydrogels [261, 262]. Like AgNPs, ZnO NPs can be embedded into the cellulose hydrogels by in situ formation or ex situ process.

In situ: CMC hydrogels were prepared by crosslinking with ECH firstly, and ZnO NPs were formed in situ oxidation of the Zn^{2+} ions within swollen CMC hydrogels. Figure 17 represents in situ formation of ZnO NPs in CMC hydrogel network. Carboxylate groups in CMC easily bind to the Zn^{2+} cations in aqueous solutions via electrostatic interactions, and the zinc ions are oxidized to ZnO NPs with the basic agent. ZnO NPs with size range of 30–40 nm were well dispersed in the hydrogels matrix at low zinc nitrate concentration, whereas some aggregation and bigger particle sizes (50–65 nm) could be seen for the CMC/ZnO composite hydrogels at higher concentration. This procedure is facile and economically not requiring heat or any other tools for NP synthesis. The prepared composite hydrogels

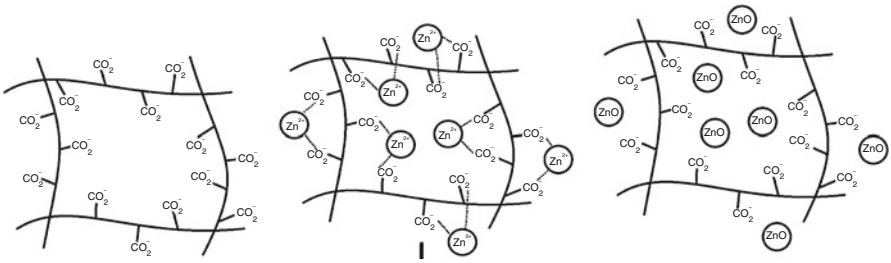

Fig. 17 The schematic representation of in situ formation of ZnO NPs in CMC hydrogel network [263]

showed pH- and salt-sensitive swelling behaviors with excellent antibacterial activity against *Escherichia coli* and *Staphylococcus aureus* bacteria [263]. The multifunctional carboxylic acids such as malic, succinic, and CA were used to crosslink CMC into hydrogels via esterification reaction between the OH group and COOH groups, and dehydration between the COOH groups and adjacent CMC molecules to give rise to strong hydrogen bonding during the thermal treatment [264].

CMC can form complexes with Zn^{2+} due to its large number of coordinating functional groups in its molecular chains, and the precipitations of nuclei start as the concentrations of Zn^{2+} and OH^{-} ions exceed the critical values. The precipitated $Zn(OH)_2$ can be transformed into the ZnO crystals via the simple chemical reaction by heat [265]. ZnO NPs/cellulose composite hydrogel particles were fabricated by using $ZnCl_2$ aqueous solution as both the solvent of cellulose and the zinc source of ZnO nanoflakes. $ZnCl_2$ aqueous solution can effectively dissolve cellulose, and reactive hydroxyl groups in the cellulose chains can accelerate the formation of ZnO nano-structures by reacting with Zn^{2+} to form $Zn(OH)_4{}^{2-}$/cellulose complex through co-gelation process and transforming to ZnO nanocrystals at low temperature. ZnO nanoflakes are hexagonal structured nanoflakes with lamellar thickness of about 100 nm. Cellulose dissolved in $ZnCl_2$ contributed not only to the growth of ZnO nanoflakes but also to restrain the formation of impurity phase [266]. Cellulose solution dissolved in NaOH/urea revealed that the sol-gel transition and intra- and intermolecular hydrogen bonds of cellulose tended to be increased as a result of its strong self-association tendency to cause aggregation and chain entanglements for the gelation [267]. ZnO NPs were grown in the network of cellulose hydrogels in situ to form the composite hydrogels [268]. Like AgNPs, ZnO was also incorporated into BC hydrogel-like pellicle by in situ synthesis of ZnO via solution plasma process without the addition of a reducing agent [269].

Ex situ: CMC was dissolved in distilled water and mixed with ZnO NPs to a homogenous solution; Fe^{3+} ion as a physical crosslinking agent was used to prepare ionic crosslinked CMC/ZnO NPs composite hydrogels by combination of metal coordination and ion exchange interaction between the carboxyl groups of CMC chains and Fe^{3+} cations. The pH-sensitive composite hydrogels showed high drug incorporation efficiency and a sustained release pattern. The release time of drugs from CMC/ZnO beads was prolonged because of a longer path to migrate from

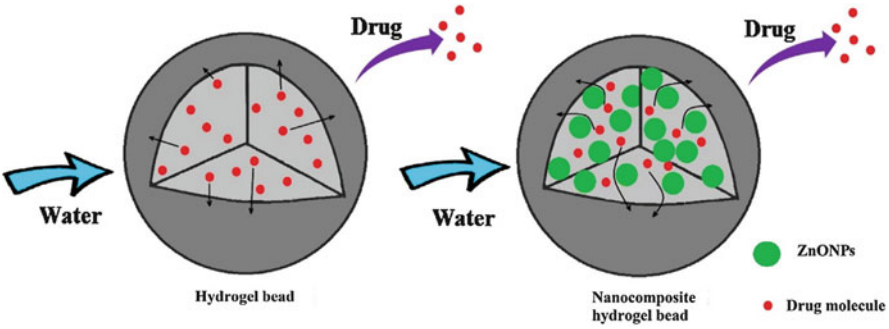

Fig. 18 The drug release of pristine CMC hydrogel and CMC/ZnO composite hydrogel [270]

hydrogels containing ZnO NPs to the buffer solution, shown in Fig. 18. The prepared CMC/ZnO NPs composite hydrogel beads might function as oral drug delivery systems for the controlled delivery of drugs [270]. In order to control the stability of the ZnO NPs, it was loaded on mesoporous MCM-41 through impregnation. ZnO-impregnated MCM-41 was added into CMC solution and further crosslinked with CA to obtain the composite hydrogels. ZnO-MCM-41 highly increased the drug loading, and addition of ZnO-MCM-41 into CMC hydrogels caused a prolonged and continued release of drugs [271]. Both ZnO and ZnO_2 NPs were loaded into the cellulose-chitosan hydrogels by dispersing the NPs into the polymer solutions before crosslinking. Cellulose and chitosan were crosslinked with triethyl orthoformate, which the primary amino group in chitosan and hydroxyl group in cellulose reacted with ethylformate, respectively. The composite hydrogels are potential new materials for tissue engineering applications with enhanced angiogenesis with zinc NPs, and it was proved that ZnO_2-loaded hydrogels supported angiogenesis better than the ZnO-loaded hydrogels because of the difference in oxidation potential [272].

4.3 Carbon Nanomaterials

Graphene and its derivates such as graphene oxide (GO) have been targeted on mechanically or electrically enhanced cellulose hydrogels as nanofillers. Specifically, GO shows the strong functionalities and processibilities due to the oxygen-containing functional groups on its basal planes and edges. The layered structure with oxygen-containing groups, i.e., hydroxyl, epoxide, and carboxyl groups, makes GO to be a favorable candidate for improving the mechanical strength of the cellulose hydrogels.

Normally, GO dispersion can be mixed with the cellulose solutions firstly and fabricated the GO/cellulose composite hydrogels further by crosslinking of cellulose. GO was mixed into cellulose dissolved in NaOH/PEG, and then the composite hydrogels were regenerated with the introduction of hydrochloric acid which neutralized NaOH and caused the reconnect and entanglement of cellulose chains by hydrogen bonds [273]. Both GO and cellulose dissolved in ionic liquids were mixed

and regenerated using water as a coagulant to composite hydrogels which significantly enhanced mechanical strength and thermal stability [274]. CMC could be chemically crosslinked with CA in the presence of GO to obtain the GO/CMC composite hydrogels, and the introduction of GO also significantly improved the adsorption performances of the composite hydrogels toward dyes and heavy metals [275]. GO/CMC-g-PAA and GO/CMC-g-PAM composite hydrogels were fabricated by in situ copolymerization of monomers on CMC backbone with MBA as a crosslinker in the presence of GO as fillers [276, 277]. GO/CMC composite hydrogels via electron beam radiation-assisted polymerization with MBA as a crosslinking agent showed larger gel fraction, higher mechanical strength and swelling capabilities compared to those prepared by solution polymerization with ECH as a crosslinker [278]. Moreover, GO and the dissolved cellulose in the NaOH/urea were crosslinked with ECH; the incorporation of GO chemically increased the compressive strength of the composite hydrogels and significantly improved their adsorption capacities for the metal ions [279].

GO/CMC composite hydrogels physically crosslinked with Fe^{3+} and Ca^{2+} ions were prepared via the coordination between metal ions and the carboxyl groups in the CMC side chains. Due to the biocompatibility and the anionic-exchange properties of GO, the composite hydrogels revealed higher loading capacity and controlled release of the drugs [280, 281]. GO/CMC/PAM composite hydrogels with double networks consisting of ionically (Al^{3+}) crosslinked CMC and covalently crosslinked PAM exhibited superior mechanical properties by combination of double networks and nanofiller reinforcement [282]. In order to decrease aggregation of GO, HPC was grafted onto GO before fabricating the composite hydrogels [283].

The recent emergence of three-dimensional (3D) graphene hydrogels has provided a promising avenue to explore the performance of 3D porous material on electrochemistry [284, 285]. GO/cellulose composite hydrogels could be fabricated by ball milling of the mixture of GO hydrogels and cellulose solution in the presence of hydrazine, template shaping, coagulating, and freeze drying. The hydrogen bond interactions and the shearing force collaboratively resulted in sufficient mixing of GO and cellulose and the subsequent formation of homogenous GO/cellulose hydrogels. It is a scalable preparation method of GO/cellulose composite hydrogels with application in supercapacitors.

GO could be incorporated into BC hydrogels with ex situ composites synthesis [286–288]; however intrinsically 3D structure of BC was broken [289]. In situ BC composites synthesis is becoming a main approach in which reinforcement materials are added to BC culture media at the beginning of the BC synthetic process. Microfibrils of BC become denser with time and produce a network structure that can trap various materials added to the BC synthetic media. The encaged materials become part of the BC fibril network, resulting in BC composites. GO/BC composite hydrogels were prepared by in situ biosynthesis of BC in graphene-dispersed culture medium. The addition of graphene reduced the crystallinity of BC without changing the entangled network structure [289, 290]. GO/BC composite hydrogels followed a non-Fickian diffusion mechanism in the drug release with good cell viability for drug delivery system [291].

Carbon nanotubes (CNTs) demonstrate very interesting properties because of sp2 hybridization of carbon-carbon bonds and the resultant cylindrical arrangement of the graphene sheets. In the realm of drug delivery, CNTs have gained tremendous attentions as promising nanocarriers, owing to their distinct characteristics, such as high surface area, enhanced cellular uptake, and the possibility to be easily conjugated with therapeutics, including both small molecules and biologics, displaying superior efficacy, enhanced specificity, and diminished side effects [292]. Carbon nanodots (C-dots) as new carbon nanomaterials have obtained increasing attentions for the applications of bioimaging, sensing, and catalysis fields, due to their exceptional properties such as highly fluorescent feature, low toxicity, excellent dispersibility in water, flexible functionalization, and good biocompatibility. C-dots possess numerous oxygen-containing functional groups on their surfaces such as hydroxyl groups, carboxyl groups, and epoxide groups, which indicate that C-dots have the promising potential application as physical crosslinkers in the preparation of NC hydrogels [293].

CNT/CMC composite hydrogels were fabricated simply by mixing CMC and CNTs at room temperature by ultrasonication; the strong hydrogen bonding as well as electrostatic interactions between acid groups of CNT and hydroxyl/carboxyl groups of CMC were believed to be the main reasons to form the composite hydrogels [294]. High-strength composite hydrogels were designed and synthesized by introducing CNTs into cellulose/NaOH/urea aqueous solution and chemically crosslinked by ECH [295]. Cellulose nanofibrils and BC were also used to fabricate the CNT/cellulose composite hydrogels [296–300].

5 Conclusions

Three categories of cellulose-based composite hydrogels were summarized in this chapter including synthetic polymer/cellulose, natural macromolecules/cellulose, and inorganics/cellulose composite hydrogels. The composite hydrogels combine the advantages of two components and obtain the new features for broadening applications especially in biomedical and tissue engineering, drug delivery, biosensors, and superabsorbent. It is feasible to incorporate some synthetic polymers with water-soluble cellulose derivatives to fabricate the synthetic polymer/cellulose composite hydrogels by chemical, physical, and ionic crosslinking. In situ free-radical polymerization of acrylate monomers onto cellulose derivatives is one of main methods to introduce synthetic polymers into cellulose-based hydrogels. Nanocellulose with high-aspect ratio can be physically entrapped in the polymer network as a filler or chemically crosslinked with the polymer matrix in order to improve the degradation and the mechanical strength of the composite hydrogels. Chitosan, alginate, starch, and extracellular matrix are popular natural macromolecules for the fabrication of natural macromolecules/cellulose composite hydrogels. Chitosan is the most important polysaccharide to form the composite hydrogels with cellulose by chemical crosslinking. Chitosan can crosslink with cellulose via crosslinkers such as epichlorohydrin or reaction between reactive groups in chitosan

and cellulose derivatives. Inorganics/cellulose composite hydrogels are a kind of special hydrogels combining both inorganic and organic properties. Montmorillonite and other layered silicates can form the nanocomposite hydrogels with cellulose for applications of superabsorbent and controlled release of nutrients. Metallic nanoparticles with inherent antimicrobial properties such as Ag were also incorporated into the cellulose composite hydrogels via ex situ and in situ methods to render antimicrobial. Carbon nanomaterials such as graphene oxide can be incorporated into the cellulose hydrogels as fillers, and the composite hydrogels show potential applications in supercapacitors and biosensors. Cellulose-based composite hydrogels are attracting considerable attentions in both academic research and industrial application due to their excellent hybrid properties.

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Surface Functionalization of Nanocellulose-Based Hydrogels

22

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Contents

Abstract

Nanocellulose is the nanostructured product or extract from the native cellulose found in plants, animals, and bacteria. Three main types of nanocellulose may be identified as cellulose nanocrystals (CNCs), nanofibrillated cellulose (NFC), and bacterial nanocellulose (BNC). Due to the very high surface-to-volume ratio,

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nanocellulose tends to form hydrogels with exceptionally high water content (>90 wt%). Surface modifications of those nanostructured materials can, e.g., improve their compatibility with different matrices, enable control of water absorption, and release and bring desired chemical functionality expanding utilization of such hydrogel in (bio)nanotechnology-related applications. Various objects including small molecules of biomedical relevance, nano- or microparticles serving as drug carriers, protective/semipermeable coatings, or polymer brushes can be attached onto the surfaces of nanocellulose-based materials in order to prepare various functional nanocomposites. Such composite materials have been successfully applied in, e.g., wound healing and regenerative medicine. Chemical approaches for surface functionalization of nanocellulose-based hydrogels are systematically described in this chapter, together with properties of such formed hydrogel materials and examples of their applications.

Keywords
Nanocellulose · Nanofibrillar cellulose · Cellulose nanocrystals

1 Introduction

Cellulose is a semicrystalline polysaccharide appearing in nature in the form of fibers of length in the range of 0.5 up to several mm [1]. From molecular point of view, cellulose is composed of β-D-glucopyranose units linked by 1-4-β glycosidic bonds, whereas at the supramolecular level, its chains aggregate and form elementary fibrils composed of alternated crystalline and amorphous domains. These elementary fibrils align and further aggregate into larger microfibrils/macrofibrils with diameter of 10–25 nm, and at the structural level, they stick together in a spiral manner to form the cellulose fibers.

Hierarchical structure of cellulose enables its breaking down into nanoscale cellulose known as nanocellulose with morphology depending on the employed extraction mode and origin of the raw material. Nanocellulose materials are commonly produced using mechanically based methods, but such nanostructured cellulose may be also produced by bacteria offering unique structural characteristics and macroscopic properties. Thus, cellulose nanocrystals (CNCs), cellulose nanofibers (CNF), and bacterial nanocellulose (BNC) are commonly distinguished within nanocellulose materials. The structure of nanocellulose implies its desired mechanical properties for reinforcing nanocomposites and enables better compatibilization due to the larger surface area as compared to typical cellulose materials. It applies especially to hydrogels due to the presence of numerous hydroxyl groups and ease of their modification on the surface of nanocellulose. The fundamentals on nanocellulose and its surface modification methods with special focus on hydrogel formation based on native and functionalized nanocellulose materials are described in this chapter together with their current and potential applications.

2 Cellulose Nanocrystals (CNCs)

Crude cellulose obtained from natural sources is composed of highly crystalline regions mixed with amorphous ones. The degree of crystallinity of naturally occurring cellulose strongly depends on its natural source. High degree of crystallinity was observed in cellulose from algae (up to 90%) and tunicate (about 80%) [2] while slightly lower in bacterial cellulose (65–79%) [3] or cellulose derived from plants (60%) [2]. Natural cellulose subjected to mechanical, chemical, and/or enzymatic treatment results in formation of highly crystalline nanomaterial devoid of amorphous regions (after proper extraction of highly crystalline regions of the cellulose microfibrils), commonly known as cellulose nanocrystals (CNCs). CNCs occur in the form of needle-shaped or rodlike particles consisting of polymer chain segments arranged in highly crystalline structure [4]. The shape, dimensions, and degree of crystallinity of CNCs are strongly determined by material's origin, as well as the method used for their isolation (see Fig. 1). The size of CNCs is usually within the range of 100 nm up to a few microns in length and 4–70 nm in width [2]. Very high aspect ratios of nanocrystals were reported for CNCs derived from maize husk (aspect ratio 157) [5] or tunicate (aspect ratio about 147) [6].

There are a few main isolation methods that lead to CNCs: acidic hydrolysis, enzymatic hydrolysis, oxidation, ionic liquid treatment, subcritical water hydrolysis, and combined processes [2]. Various isolation methods have been presented in details in several review papers [2, 4, 7]; therefore only brief description of acidic and enzymatic hydrolysis will be provided below. Acidic hydrolysis is the most

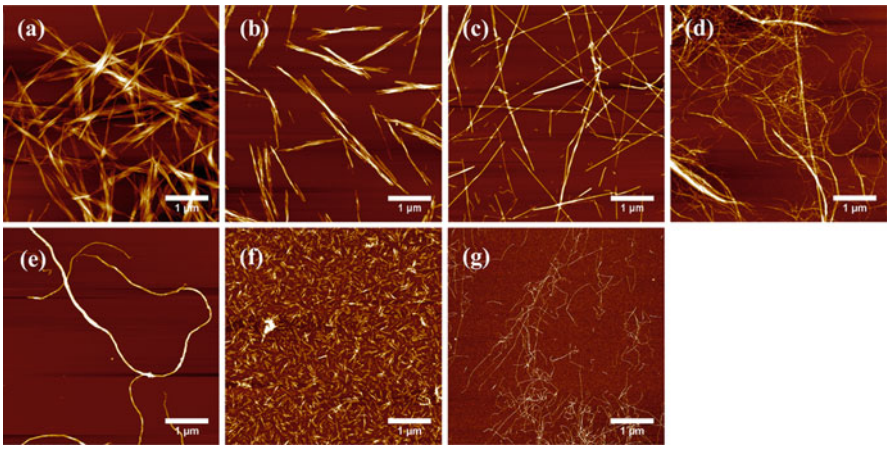

Fig. 1 AFM topography images of CNC derived from bacterial cellulose after HCl (**a**) and after H_2SO_4 treatment (**b**), tunicate cellulose after H_2SO_4 treatment (**c**), wood cellulose after enzymatic (**d**), mechanically refined (**e**), H_2SO_4 (**f**), and TEMPO (**g**) treatments. (Reprinted with permission from Ref. [6])

popular approach among all isolation methods. This process is based on strong acid-induced removal of the amorphous parts in the cellulose microfibrils. Strong acids may preferentially and easily hydrolyze amorphous regions, due to their low level of order, leaving the crystalline regions unaffected [4]. The selection of the acid plays an important role as it determines the properties of the final material. The most popular hydrolysis with sulfuric acid [8, 9] results in formation of CNCs with negative surface charge (due to sulfonation of CNC surface), which may easily form stable colloidal suspension useful for various applications. However, CNC sulfonation promotes degradation of cellulose at higher temperatures [2]. Utilization of hydrochloric acid ensures higher stability but lower charge density at CNC surface and, as a result, poorer dispersibility in aqueous media [1]. Very recently Chen et al. [10] demonstrated that organic acid applied in cellulose hydrolysis resulted in formation of CNCs with moderate dispersibility in water and significantly higher thermal stability than that produced using sulfuric acid.

The process of acidic hydrolysis requires the use of hazardous and toxic materials during CNC production, while enzymatic hydrolysis is much safer and environmentally friendly. As enzymes are much more selective and milder agents, they do not destroy crystalline parts and enable formation of materials with original hydroxyl surface chemistry. However, such treatment ensures lower synthesis yields [11] and it is much slower than acidic hydrolysis.

2.1 Low Molecular Weight Modifications of CNC

CNC surface may be modified in three different ways. The first approach utilizes surface functionality introduced during CNC isolation. As it was mentioned above, depending on the isolation method, CNC surface bears various groups such as sulfate esters after sulfuric acid isolation, hydroxyl after enzymatic or hydrochloric acid treatment, and carboxyl after oxidative isolation in the presence of 2,2,6,6-tetramethyl-piperidinyl-1-oxyl (TEMPO) radicals [12]. Therefore, the choice of isolation method determines surface chemistry of CNC, as well as further synthetic paths for grafting of particular molecules.

The second method is based on adsorption of particular compounds to the surface of CNC. Different surfactant molecules such as stearic acid [13], cetyltrimethylammonium bromide (CTAB) [14], and quaternary ammonium-based compounds [15] were used in such approach in order to increase dispersibility of CNCs in organic solvents and polymers.

The last approach utilizes covalent grafting of particular molecules on the cellulose surface. Figure 2 shows the most frequently used methods for covalent grafting of various low molecular compounds. Hydroxyl groups on CNC may be easily reacted with chloro- and alkoxysilanes [16], isocyanates [17], acid halides [18], acid anhydrides [19], or epoxides [20]. CNCs modified by oxidation of hydroxyl groups (to carboxyl ones) are commonly applied as precursors for amidation reaction [21]. Carboxyl groups in such synthesis are activated in the first step by *N*-hydroxysuccinimide (NHS) and then are reacted with primary amines leading to

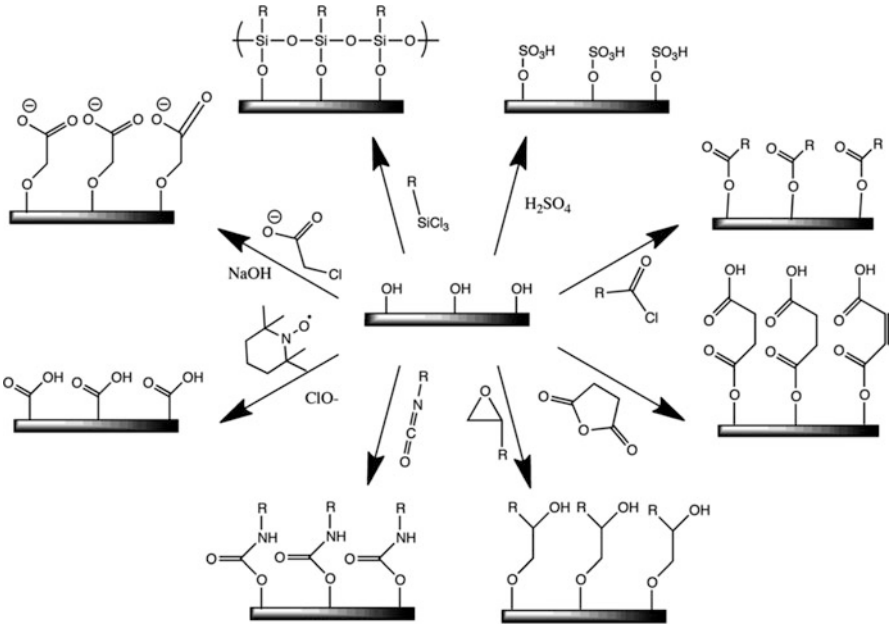

Fig. 2 CNC surface modifications during selected isolation methods together with common synthetic paths to low molecular compound grafting. (Reprinted with permission from Ref. [7])

amides [22]. The mentioned procedure was used also by Filpponen et al. for the synthesis of alkyne-based CNC precursors for the click reaction [23]. It is important to underline that the diversity of modification techniques is far greater, as the presented surface functionalizations may serve as precursors for further modifications.

2.2 Modifications of CNC with Polymers

Cellulose nanocrystals may be functionalized with polymers via either covalent grafting ~~and~~ or adsorption. Electrostatic adsorption of polymers on cellulose enables formation of composite thin films via layer-by-layer (LbL) technique [24]. Very recently Gill et al. prepared LbL-coated CNC (isolated using sulfuric acid-based hydrolysis) containing films with xyloglucan (XG) and polyethyleneimine (PEI) [25]. Interactions responsible for LbL film formation were based on van der Waals forces in XG/CNC system, while for PEI/CNC they were of electrostatic nature. Furthermore, CNC surface is prone to adsorption of amphiphilic polymers as presented by Zhou et al. [26]. The authors showed modification of CNC via adsorption of xyloglucan oligosaccharide-based triblock amphiphilic copolymer. The resulting material exhibited chiral nematic self-ordering of the CNCs with the adsorbed copolymer. Recently Nagalakshmaiah et al. presented surface adsorption of amphiphilic triblock copolymer based on two hydrophilic polyethylene oxide

blocks and one hydrophobic polypropylene oxide block [27]. The applied modification increased thermal stability and aqueous dispersibility of CNCs.

Covalent attachment of polymer chains to CNC is more frequently used and is realized by three main strategies called "grafting through," "grafting to," and "grafting from." First of them is based on grafting via surface-anchored monomer or macromonomer. In this approach polymerization mainly proceeds in solution, and the macromolecules growing there may react with surface-anchored monomers resulting in polymer grafting. This methodology leads to grafted polymers with wide molar mass distribution and low grafting density. "Grafting through" approach represented by free radical polymerization was applied by Atifi et al. for grafting poly(acrylamide) on CNC surface [28]. In the "grafting to" approach, end-functionalized polymer chains are at first synthesized in the solution. Such prepared macromolecules are then subjected to grafting on CNC surface. Attachment of polymers using "grafting to" method utilizes the same chemistry as presented in Sect. 2.1 concerning covalent grafting of low molecular compounds. However, formation of densely packed polymer brushes using this strategy is hindered due to steric impediment created by already attached polymer chains that block active sites on the surface. The main advantage of "grafting to" is the fact that macromolecules synthesized in the solution may be carefully characterized using different methods (not available for grafted polymers) before grafting. Cellulose nanocrystals were modified with different polymers via "grafting to" methodology using click chemistry (CNC-g-poly(ethyl ethylene phosphate)) [29], amidation (CNC-g-polypeptides) [30], or etherification (CNC-g-(poly(ethylene oxide))) [31].

"Grafting from" approach is a first choice method for covalent grafting of polymers on CNC surface. It starts from the initiator-modified surface and utilizes well-controlled surface-initiated reversible-deactivation radical polymerizations (SI-RDRP) such as atom transfer radical polymerization (SI-ATRP), nitroxide-mediated polymerization (SI-NMP), or reversible addition-fragmentation chain transfer (SI-RAFT) [32]. Controlled character of SI-RDRP techniques is due to very fast and reversible activation and deactivation processes of the growing radicals. Instead of SI-RDRP, surface-initiated ring opening polymerization (SI-ROP) may be also applied for polymer attachment via this approach. This methodology enables formation of well-ordered and densely packed brushes. In the most popular SI-ATRP technique, CNC surface is predominantly directly modified with ATRP initiator via esterification reaction (e.g., with α-bromoisobutyryl bromide). Polymerization is started from the initiator-decorated CNC in the presence of monomer, solvent, and activation complex (in basic ATRP composed of transition metal salt and chelating ligand) which ensure controlled character of the process [32]. The description of the mechanism of SI-ATRP and the abovementioned polymerization is beyond the scope of this chapter; therefore only short overview of the very recent CNC modifications done via SI-RDRP and SI-ROP is given below. Comprehensive information is collected in the review papers [32, 33].

SI-ATRP was used for polymerization of styrene from CNC surface in order to increase thermal stability and compatibility of the native material with other polymers [18]. Similarly, Zhang et al. presented a synthetic route for grafting

thermoresponsive poly(*N*-vinylcaprolactam) on CNC using SI-ATRP. Roeder et al. reported for the first-time graft modification of CNCs via SI-NMP [34]. Cellulose surface was functionalized with (4-(diethoxyphosphinyl)-2,2,5,5-tetramethyl-3-azahexane-N-oxyl) (SG1 nitroxide) which served as the initiator. Poly(methyl acrylate) and poly(methyl methacrylate) brushes were then successfully obtained under relatively mild reaction conditions. SI-RAFT method was used for surface-initiated polymerization of vinyl acetate, which resulted in the formation of CNC composite material with promising mechanical properties [35]. SI-ROP technique was also applied for formation of polymer composites with improved mechanical properties. For this purpose CNCs were decorated with poly(L-lactide) and incorporated in poly (lactic acid) matrix [36].

2.3 Hydrogels Containing CNC

High stiffness and mechanical strength of CNCs are recognized as desirable features for creation of stable hydrogel nanocomposites. Lahiji et al. indicated that transverse elastic modulus of an individual cellulose nanocrystal is a few times higher than for Kevlar-49 and it lies in the range of 11–57 GPa [37]. The mentioned traits of CNCs, together with low ability to entangle, unfortunately, hinder formation of single-component CNC gels [38]. However, high concentrations of CNCs in their aqueous suspensions (above 10–12 wt%) may result in formation of gel-like phase [39]. Nevertheless, addition of salts, acids, or multivalent ions may extort gel formation due to destabilizing effect on CNC suspension. It was reported that increased ionic strength of CNCs aqueous suspension led to gelation at significantly lower concentrations of CNCs (about 2 wt%), as addition of salt-limited electrostatic repulsions between particular nanocrystals while promoted their mutual attractive interactions by hydrogen bonding and van der Waals forces [40]. Single-component CNC hydrogels can be also obtained via pH-induced gelation, thanks to modifications of nanocrystal surface with amine or carboxyl groups [41].

In fact, multicomponent hydrogels with CNC as filler or reinforcing agent within polymeric networks have aroused the greatest interest so far [38]. Such nanocomposite hydrogels are produced via physical or chemical entrapment of native or functionalized CNCs by polymeric matrix. The former approach is represented by various synthetic methodologies such as free radical polymerization of monomers within CNC suspension, homogenization, and physical entanglement of polymer networks or UV-mediated cross-linking of the polymeric network around CNCs. Free radical polymerization of sodium acrylate in nanocrystal suspension in the presence of the cross-linker, *N*,*N*-methylenebis-acrylamide, was applied for formation of poly(sodium acrylate) hydrogels with physically entrapped CNCs [42]. Agarose hydrogel with cellulose nanocrystals as a filler was prepared via homogenization process by Osorio-Madrazo et al. [43]. The orientation of cellulose rodlike particles within agarose matrix was found to be dependent on drying process and hydrogel stretching.

In the case of chemical entrapment, CNCs can serve as polymer cross-linkers themselves, while in other cases CNCs are cross-linked to a networked polymer matrix [38]. Yang et al. have presented formation of poly(*N*,*N*-dimethylacrylamide) (PDMA) hydrogel with chemically entrapped nanocrystals via UV-initiated free radical polymerization of *N*,*N*-dimethylacrylamide in CNC suspensions [44]. In the first step, CNC surface was modified with organosilane-bearing methacryloyl group, and then, in the second step, they were subjected to UV-initiated polymerization in the presence of monomer and photoinitiator. As a result CNC-PDMA hydrogel with significantly improved mechanical properties was formed due to combination of chemical cross-linking and physical interactions between modified nanocrystals.

Concentration of CNC in multicomponent hydrogels is usually in the range of 0.1–6 wt% (in reference to the total swollen gel weight). De France et al. reported that poly(oligoethylene glycol methacrylate) (POEGMA) hydrogel with relatively low CNC concentration (4.95 wt%; hydrogel with physically entrapped CNCs) demonstrated about 35 times higher storage modulus (39 kPa) than initial POEGMA hydrogel (1.1 kPa) [45]. Hydrogels with chemically entrapped CNCs generally present lower swelling ability and better mechanical stability than those obtained by physical entrapment methods (as reinforcement effect is more pronounced for similar systems). Mechanical strength of CNC-reinforced hydrogels was found to depend on the content of nanocrystals and aspect ratio as found by Yang et al. [44, 46]. Poly(acrylic acid)-based hydrogels reinforced with chemically entrapped CNCs with different aspect ratios were obtained. The authors have found that hydrogel storage modulus significantly increased together with the growing aspect ratio of the nanocrystals [46].

2.4 Applications of CNC

Surface hydroxyl groups, high surface area, high stiffness, and tensile strength of cellulose nanocrystals make them very attractive nanomaterials for various applications. As-synthesized CNCs (functionalized or nonfunctionalized) can be applied as antibacterial agent (CNCs modified with Ag nanoparticles) [47], adsorbents (carboxylated CNCs were found to present specific adsorption for methylene blue dye) [48], Pickering emulsifier [49], highly transparent nanopaper for flexible electronics [50], or pH sensor (CNC surface modified with pH indicator dye) [51]. However, most of CNC applications are related to their use in different polymer composites, e.g., for drug delivery systems [52], biosensors [53], separators for energy storage [54], biodegradable food packaging materials [55], and transparent conductive membranes [56]. There are a few review papers that gathered most of CNC applications [4, 7, 57], but we focus here on applications of CNCs in formation of hydrogels. Alginate/gelatin hydrogels with CNCs as reinforcing agent were used as injectable tissue scaffolds by Wang et al. [58]. The addition of CNCs reduced degradation of the hydrogel and positively influenced long-term cell proliferation. Very recently Lin et al. have synthesized biocompatible dual-membrane hydrogel

composed of cationic CNCs and anionic alginate [59]. The external membrane was composed of neat alginate, while the internal one contained the hydrogel composed of cationic CNCs and anionic alginate. Two drugs were introduced into those membranes and different drug release characteristics were observed. The authors have demonstrated rapid release of the drug from the outer neat alginate membrane, while prolonged drug release from the inner hydrogel-based one was induced by steric effect resulting from the strong interactions between cationic CNCs and anionic alginate. Recently Zubik et al. have developed CNC/PNIPAM poly(*N*-isopropylacrylamide) thermoresponsive hydrogel with incorporated metronidazole drug for wound dressing applications [60].

CNC hydrogels have found applications not only in the biomedical field. Kelly et al. developed CNC-based responsive photonic hydrogels which had long-range chiral nematic structure [61]. Depending on the applied polymer matrix, materials show changes in iridescence in response to solvent type, pH, and temperature. McKee et al. synthesized three-component hydrogel composed of reinforcing CNC colloidal rods modified with copolymer brushes (via SI-ATRP) bearing naphthyl (guest) group, linear polymer containing methyl viologen functionality (additional guest group), and macrocyclic supramolecular cross-linker (cucurbituril [8], host group), which allowed host-guest interactions leading to selective and simultaneous binding of two guest groups [62]. The obtained supramolecular nanocomposite hydrogel exhibited rapid sol-gel transition (<6 s), high storage modulus (above 10 kPa), and self-healing properties maintained upon aging for even several months.

3 Nanofibrillated Cellulose (NFC)

The cellulose nanofibers are mainly produced by mechanical breaking out the cell wall of fibers and releasing the cellulose fibrils in the form of bundles of elementary fibrils [63, 64]. Nanofibrillated cellulose (NFC), cellulose nanofiber, and cellulose nanofibril are the terms commonly used for the same material [65]. Being composed of a bundle of stretched cellulose chains with long and entangled nanofibers of approximately 1–100 nm in diameter, NFC consists of alternating crystalline and amorphous domains [66]. In order to perform the defibrillation of NFC, intensive mechanical treatment is required. However, depending on the degree of processing and raw material, chemical pretreatments are carried out before mechanical defibrillation [67]. Appropriate pretreatments of cellulose fibers are of great interest since they induce breaking of hydrogen bonds, promote accessibility of hydroxyl groups for modifications, and therefore boost their reactivity [68].

As introduced by Turbak and coworkers in the 1980s [69], the high-pressure homogenization and microfluidization are still the main methods currently used to effectively produce NFC [70, 71]. They include simple mechanical methods, sometimes in combination with enzymatic or chemical pretreatments. The process of isolating NFC consists of disintegration of cellulose fibers along their long axis into substructural fibrils having lengths in the micron scale and widths in the range from

ten to a few hundred nanometers depending on the nature of the plant cell walls [72]. That obtained aqueous suspensions exhibit gel-like features in water with pseudoplastic and thixotropic characteristics even at low solid content. Other technologies, namely, high-intensity ultrasonication [73], high-speed blending [74], and stem explosion [75, 76], were also proposed, but they are still in a very early stage of development and far from scaling up. Employing the abovementioned technologies, NFCs were prepared from numerous cellulosic sources including soft and hard woods [77], sugar beet pulp [78], banana [79], wheat straw [80], bamboo [81], and seaweed [82]. The morphological properties of the resulting NFCs are strongly dependent on the original fibers, and the general tendency is that NFCs from primary cell wall fibers are longer and thinner than those obtained from secondary cell wall fibers.

It should be emphasized that, in spite of very promising potential of multimode applications of NFCs, their scale-up production is still below expectation. One of the major limitations of this development is high energy consumption involved during the mechanical disintegration of cellulose into nanofibers [83]. In addition, fabrication of uniform size NFCs is also challenging. The energy consumption strongly depends on the fiber pretreatment method, and reported values range from 10 up to 100 KWh per kg of dry NFC [84]. This high energy demand is connected with the necessity to operate under high pressure (200–800 bar) with multiple passes until a high fibril ratio degree is achieved. To cope with this issue, the fiber pretreatment prior to the disintegration process is commonly adopted. In this field, the chemical pretreatment seems to be one of the most efficient and popular strategies to enable the breakup of the fiber network by producing ionic or ionizable groups within the internal structure of the cellulose. There are many methods like TEMPO-mediated oxidation [85], carboxymethylation [86], sulfonation with sodium bisulfate [87], periodate oxidation [88], or quaternization [89] which enable to achieve that goal. Another advantage of the pretreatment is the reduction of the risk of clogging during the homogenization/microfluidization processes. It was found that chemical pretreatment approach can significantly reduce the energy consumption for production of NFC; however in many cases, the price of chemicals surpasses the energy costs saved.

3.1 Low Molecular Weight Modifications of NFC

Surface modification of NFCs is essential when considering improvement of their compatibility and homogeneous dispersion within polymer matrices. Both low and high molecular weight modifications, such as polymer grafting, silylation, esterification, cationization, or TEMPO oxidation, have been applied for that purpose [90].

Lu et al. reported the surface modification of nanofibrillated cellulose by use of silane reagents, namely, 3-aminopropyltriethoxysilane and 3-glycidoxypropyltrimethoxysilane [91] leading to formation of Si-O-C bonds at room temperature through –OH groups of cellulose. The wettability of the surface of pristine and modified NFC was investigated, and it was revealed that untreated NFC film was very hydrophilic with the water contact angle of 15° resulting from OH-rich molecular structure. The

silane modification of NFC increases the value of water contact angle to 90° and 64° for 3-aminopropyltriethoxysilane and 3-glycidoxypropyltrimethoxysilane-treated NFC, respectively. NFC was also hydrophobized via partial surface silylation using isopropyl dimethyl chlorosilane as a silylation agent, and it was found that loss of nanostructure occurred when silylation conditions were too harsh [92].

Acetylation is another method adopted by the researchers to modify the surface of cellulose nanofibers. It is based on chemical modification in which acetyl groups react with the hydroxyl groups of the cellulose, making the surface more hydrophobic. Acetylation of NFC was performed to change the wettability of cellulose nanofibers and, as a consequence, to improve the chemical affinity between NFC and nonpolar environments. It was observed that the acetylated nanofibers, being more hydrophobic, formed stable suspension in solvents like acetone or ethanol, while the pristine NFC exhibits tendency to sedimentation in these applied solvents [93]. Tingaut and coworkers studied the impact of acetyl content on the dispersion stability and the influence of chemical modification on the crystal structure of NFC [94]. They found that the obtained powdered nanofibers were easily redispersed in chloroform and formed very stable suspensions. They also observed variations in NFC stability which depended on the percentage (%) of acetylation (Ac); stable suspensions were obtained for NFC with more than 1.5% acetylation. Using wide-angle X-ray diffraction (WAXD) analysis, Tingaut et al. showed that more than 4.5% of Ac strongly affected NFC crystalline structure since grafted acetyl groups caused reduction of hydrogen bonding between the cellulose fibrils.

Cationic modification of NFC films was performed by adsorption of cationic surfactant cetyltrimethylammonium bromide (CTAB) [95]. Employing high-resolution transmission electron microscopy (HRTEM), it was demonstrated that the CTAB molecules adsorbed on the nanofibril surfaces. That was manifested by the presence of black dots (surfactant molecules) only along the surface of nanofibril of modified NFC (see Fig. 3).

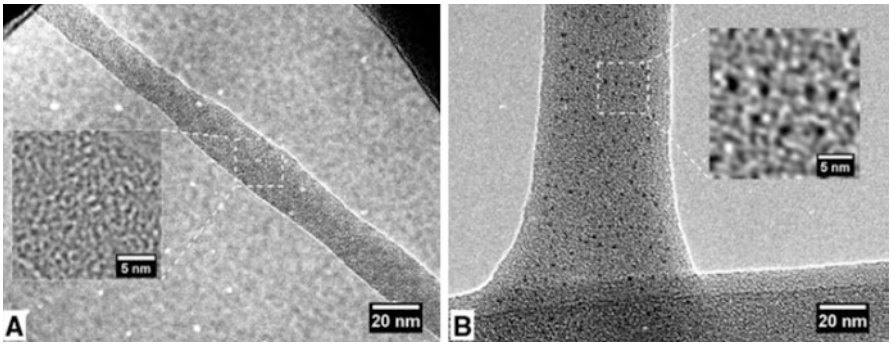

Fig. 3 (**a**) HRTEM of a single nanofibril. (**b**) HRTEM image of a CTAB-modified nanofibril. Note that the images (**a**) and (**b**) were taken at the same magnification, i.e., 100,000. The contrast of the images has been modified for better visualization. (Reprinted from Ref. [95] with permission from Springer)

Yano and coworkers reported on alkali treatment of NFC by immersing the dry sheets of NFC in NaOH aqueous solutions of two concentrations (5 and 20 wt.%). The dispersion was kept at reduced pressure of 0.01 MPa for 2 h and subsequently at ambient pressure for 10 h. It was found that the NFC sheets modified with 5 wt.% NaOH solution did not reveal any changes in dimensions, while 20 wt.% alkali solution treatment resulted in a noticeable reduction in diameter of about 17% as compared to unmodified NFC [96]. Seppala et al. using click chemistry synthesized pH-responsive 1,2,3-triazole-4-methanamine decorated NFC [97]. Reactive azide groups were introduced on the surface of NFC by the etherification of 1-azido-2,3-epoxypropane in alkaline water/isopropanol mixture at ambient temperature. Subsequently the reaction between azide-functionalized NFC and propargyl amine using copper-catalyzed azide-alkyne cycloaddition (CuAAC) was performed to introduce amine groups.

3.2 High Molecular Weight Modifications of NFC

Several studies have reported on graft copolymerization onto NFC. Xiao and coworkers focused on the creation of controllable hydrophobic chains on NFC employing SI-ATRP of butyl acrylate [98]. Li et al. similarly grafted poly(butyl acrylate) (PBuA) on NFC for subsequent application in reinforcement of a biocomposite [99]. A two-step method for grafting polyacrylic acid (PAA) onto cellulose nanofibers was developed by Vega et al. [100]. In the first stage, the cellulose fibers were treated with an epoxide that contains a terminal double bond and subsequently grafting of the PAA onto the cellulosic fibrils with potassium persulfate as a reaction initiator was carried out. Another approach to improve the dispersibility of the hydrophilic NFC in the nonpolar matrix and the interfacial adhesion in the composite material was based on grafting of poly(ε-caprolactone) (PCL) via ring-opening polymerization of ε-caprolactone [101].

Properties of pristine NFC and acrylic monomer-grafted NFC were investigated by AFM technique [102]. It was found that the grafted NFCs exhibit a rougher surface than those of the unmodified NFC; however nanoscale fibrillar structure was retained during the graft copolymerization process. AFM images revealed that the fibrils of the grafted NFC were thicker when compared to those of the pristine sample. This was explained considering large amount of polymer grafted on the NFC surface. In the case of NFC modified with poly(glycidyl methacrylate) (PGMA) with 80% of weight fraction of the grafted PGMA was clearly visible as a granular structure on the nanofibrils. NFC grafted with PGMA and poly(methyl methacrylate) (PMMA) formed a stable dispersion in acetone and THF.

3.3 NFC-Based Hydrogels and their Applications

Design of cellulose-based hydrogels, which combines biodegradability with smart stimuli sensitive behavior, is of great interest [103]. The ability of cellulose to absorb

large amounts of water makes it attractive material in fabrication of various hydrogels. Many factors affect the ability of cellulose to absorb water, and among them the most important are degree of crystallinity, total surface area, and pore volume [104]. NFC with its large surface area, water retention value, transparency, and sustainability is considered as a promising candidate for hydrogel-based material construction [105].

However, the low mechanical characteristics of the NFC native hydrogel – with storage modulus around 10 Pa at 0.5 wt% [106] – significantly limit its application in soft tissue engineering [107, 108]. In order to improve the mechanical strength of the NFC hydrogel, chemical cross-linkers such as ethylenediamine or hexamethylenediamine have been applied; however they might bring the risk of some cytotoxicity [109, 110]. Environmentally friendly methods to adjust the mechanical properties of NFC hydrogel for potential applications in tissue engineering were achieved by controlling the hydrogel swelling capacity [111] or by introducing biocompatible reinforcing agent such as hemicellulose [112]. Liu et al. applied two approaches to use hemicelluloses as cross-linkers to tune the structural and mechanical properties of NFC hydrogel scaffolds and investigated the effect of these properties on the cellular behavior during wound healing application. Different types of hemicellulose, namely, galactoglucomannan (GGM), xyloglucan (XG), and xylan, were introduced into NFC network via presorption and in situ adsorption to reinforce the NFC hydrogels. They reported that the charge density of NFC, type and amount of incorporated hemicellulose, and the swelling time of the hydrogels affected the pore structure, the mechanical strength, and thus the cells' growth on the composite hydrogel scaffolds. Among all employed hemicelluloses, the XG showed the highest adsorption capacity on the NFC and the highest reinforcement effect, and it promoted cell growth. The conclusion was that the polysaccharide composite hydrogels fabricated by presorption method may work as promising scaffold in wound healing applications to provide supporting networks and to promote cells adhesion, growth, and proliferation.

Recently, there has been great interest in the use of NFC in improving the physical properties of hydrogels. Owing to large surface area and high stiffness and strength, NFC has been used to reinforce various polymer matrices, like poly(styrene-co-butyl acrylate) and poly(vinyl acetate) latexes [113], polyurethane [114], hydroxypropyl cellulose [115], and poly(lactic acid) [94]. Nair and coworkers [116] developed nanocomposite hydrogels based on nanofibrillated cellulose cross-linked with poly (methylvinylether-co-maleic acid) and polyethylene glycol. The resulted hydrogels showed enhanced water sorption and gel content with the addition of nanocellulose. Moreover, the thermal stability, mechanical strength, and modulus increased with an increase in the amount of nanocellulose in the hydrogels. It was explained considering the efficient cross-linking between the nanocellulose and the matrix. The improved physical characteristics confirmed that by cross-linking interactions between the NFC and polymeric matrix distinctively unique hydrogels that are not just blends of starting materials are formed.

Eyholzer et al. fabricated biocomposite hydrogels with carboxymethylated, nanofibrillated cellulose (c-NFC) powder by UV polymerization of N-vinyl-2-

pyrrolidone with Tween 20 trimethacrylates as a cross-linking agent [117]. This composite was designed to serve for replacement of the native, human nucleus pulposus (NP) in intervertebral disks. The swelling ratios and elastic moduli of neat and biocomposite hydrogels were investigated for various c-NFC concentrations and degree of substitution. The resulted biocomposite hydrogels were shown to successfully mimic both the mechanical and swelling behavior of the NP. Moreover, the presence of the c-NFC in hydrogels improved material relaxation properties compared with neat hydrogels, what was demonstrated by lower strain values after cyclic compression tests.

Wen et al. developed superabsorbent composites based on poly(acrylic acid)/nanofibrillated cellulose [118]. NFC was introduced to the system during the UV-induced polymerization process of acrylic acid, so that the obtained composites can reveal enhanced water absorbency and swelling rate. It was demonstrated that even on addition of a small amount of NFC, substantial increase in both water absorbency and swelling rate of the PAA/NFC hydrogel composite was observed. The water absorbency of the obtained composite increased from 380 to 525 g/g at 1 wt% of NFC addition, whereas the swelling rate in deionized water increased by 25% when compared to the control.

In the recent years, NFC-based hydrogels were successfully used by many researchers, especially in the field of various biomedical applications. Nanofibrillated cellulose composite hydrogel was developed for the replacement of NP [117, 119]. It was reported that composite hydrogels reinforced with cellulosic nanofibers can be potentially useful as NP implants. It was shown that their satisfactory swelling ratio may restore the annulus fibrosus loading, while enhanced mechanical properties could possibly restore the height of the intervertebral disks. NFC was also applied as a material for the development of nanocomposite scaffolds for use in artificial ligaments or tendon substitutes [120]. It was found that resulted nanocomposites exhibited excellent cytocompatibility required for biomedical applications and mechanical properties similar or better than the natural ligaments and tendons. Cellulosic nanofibers were also employed to reinforce collagen-based implantable scaffolds, what resulted in better mechanical properties and dimensional stability without affecting the biocompatibility of pristine collagen [121]. NFC-based hydrogels were also studied for potential wound healing applications. It was demonstrated that NFC is non-cytotoxic [109] and exhibits ability to impair growth of common wound bacteria [122] and to reduce inflammation and promote wound healing [108]. All these qualities are suitable for wound healing applications.

The high swelling ability of the NFC hydrogels opens the opportunity to incorporate biomolecules, e.g., peptide, nucleic acids, enzymes, or even whole living cells, into their porous structures for future release or supporting cellular processes in biomedical applications. The adjustable porous structure and stiffness of the NFC-based materials can therefore meet the required pore size and mechanical strength for various cellular activities, such as cell adhesion, proliferation, as well as transportation of nutrients and metabolites [123].

4 Bacterial Nanocellulose (BNC)

Nanocellulose produced as a result of bacterial biosynthesis (BNC) stands out as chemically very pure and structurally significantly different from the nanocellulose obtained from plants. The structure of BNC can be described as a reticulate network of fine fibers with the diameter of 0.1 μm, which is about 100 times smaller than that of plant-derived fibers. BNC shows the whole spectrum of desired properties, including high degree of crystallinity, high density, good shape retention, and high water-binding capacity, which makes it a perfect material for various applications in textile, paper, and food industries, waste treatment, broadcasting, mining, and refineries [124]. Recently a special attention is given to its possible utilization as a biomaterial in tissue engineering, wound dressings, drug delivery, and vascular grafts. Due to high requirements imposed on biomaterials for advanced biomedical applications, most of the currently developed BNC modifications are focused on this area of research.

4.1 BNC Modified with Low Molecular Weight Compounds

Due to its high purity, chemical stability, good mechanical properties, excellent biocompatibility, and ability to form hydrogels, BNC meets practically all the requirements of materials for the modern wound dressing. It does not, however, possess any bacteriostatic or antimicrobial activity, which seems a key property, especially in dressings used in chronic wounds. Various low molecular weight compounds were introduced on BNC surface or entrapped inside its matrix in order to solve this issue, including ibuprofen [125], benzalkonium chloride [126], or silver sulfadiazine [127]. One of the most promising compositions for chronic wound healing seems to be combining BNC with octenidine. The latter is a cationic surfactant known for its broad antimicrobial activity against both Gram-positive and Gram-negative bacteria, as well as plaque-forming bacteria, and fungi. It possesses excellent skin compatibility and does not induce resistance [128]. Moritz et al. [129] introduced octenidine into the BNC matrix by 48 h incubation of the BNC fleeces with 0.5% aqueous solution of octenidine at 20 °C with constant mixing (70 rpm). SEM analysis demonstrated that the presence of the drug, confirmed by weight increase of the samples, did not change the structure of BNC. Octenidine release was followed using spectrophotometry. Release profile was exponential with high initial burst (up to 82% of the drug) within the first 8 h. The equilibrium conditions were reached after 24 h and the total release was around 92%. The rapid release of the significant amount of loaded octenidine should allow to effectively eliminate bacteria and other microbials and seems advantageous. On the other hand, the fact that release has practically stopped after only 24 h is not preferable, especially for long-healing chronic wounds, as the frequent dressing change should be rather avoided. Authors performed also the stability tests over up to 6 months, combined with tests of antimicrobial activity of the new and aged samples. The aluminum

packaging was chosen as the optimal for the wet modified BNC fleeces, as it allowed not only to protect the content from the microbials invasion but also to prevent the loss of moisture. The tests performed for the fresh samples, as well as these stored in aluminum foil for 3 and 6 months, showed no significant difference in their performance in respect to octenidine release profile and antimicrobial activity. The authors made also an attempt to upscale the BNC dressing and concluded that the most important parameters, which may change the drug release profile and overall performance of the material, are surface-to-volume ratio and water content.

Another approach to effectively control the release profile has been studied recently in our laboratories [130]. Curcumin, the natural polyphenol, known for its anti-inflammatory and antimicrobial activity, was reported to exhibit wound healing properties upon topical application [131]. Because of its low solubility in aqueous media and relatively low stability in physiological conditions, we proposed to entrap curcumin in the polysaccharide submicroparticles formed from the composite of sodium alginate and hydroxypropyl cellulose. To facilitate the introduction of the hydrophobic compound into the hydrogel matrix, Pluronic® P103 micelles were used. The encapsulation efficiency and release profile could be adjusted based on the particle's composition and their formation procedure. Chitosan outer coating was added in order to both further modify the release and allow the covalent attachment of the particles to BNC surface. Particles were characterized using SEM and AFM and demonstrated to have regular round shape and average diameter of 0.35 μm. The amide covalent bond formation between chitosan amine groups and hydroxyl groups of BNC was confirmed by FTIR analysis with attenuated total reflectance (FTIR-ATR) accessory. The attachment process had no influence on the curcumin release profile, which was favorable due to initial burst of the drug followed by prolonged, slower release for up to 5 days.

Alongside the BNC modifications with small organic molecules, mainly drugs, the BNC composites with inorganic compounds were also studied. Janpetch et al. [132] proposed BNC-ZnO hybrid composite designed for antibacterial applications. Solution plasma process, developed by Tokai [133], was used to simultaneously generate ZnO particles and deposit them onto the BNC pellicle. BNC was first saturated with methanol to remove surplus water from the hydrogel and then incubated for 24 h in Zn^{2+} ion solution in methanol. The resulting BNC pellicles containing zinc ions were introduced into a solution plasma glass reactor containing methanol, and the plasma treatment was conducted for 1 h. Chemical composition was studied using X-ray photoelectron spectroscopy (XPS). Characteristic peaks for BNC fibers (C 1 s at 285 eV) and hydroxyl groups (O 1 s at 530 eV), as well as those originating from Zn-O bond (Zn 2p3/2 at 1022 eV) and Zn core (Zn 2p1/2 at 1045 eV), were found in the spectrum of the resulting material. The results were confirmed by energy-dispersive X-ray (EDX) and FTIR-ATR analyses. SEM analysis have shown rodlike shape of the ZnO deposited on BNC surface. If zinc acetate was used instead of zinc nitrate as ZnO precursor, the resulting ZnO deposit had dense multilayered structure. Authors concluded that the antibacterial activity of BNC-ZnO composite depends on the type and concentration of zinc ion precursor, the method used to synthesize ZnO deposited on BNC, and bacteria strain used in

tests. This material was proposed for wastewater treatment, but the authors suggest possibility of biomedical application after further safety studies.

4.2 BNC Modified with High Molecular Weight Compounds

As mentioned before, BNC can be applied as a component of wound dressings, which require relatively high stability and good mechanical characteristics. Ability to retain wound exudates and activity against microbials are also of great importance in these materials, especially when applied to chronic wounds, as ongoing inflammation due to the presence of certain bacteria can compromise the healing process. Chitosan, a naturally occurring polysaccharide, is well known for its unique properties such as high biocompatibility and ability to form hydrogels and significant antimicrobial activity. Zhang et al. [134] have proposed the new wound dressing formed by incorporating chitosan (CS) into the BNC matrix with additional strengthening by the addition of fabric (cotton gauze). The material was obtained in situ in the culture of *Gluconacetobacter xylinus ATCC 23770* strain by either static cultivation for 10 days or by using dynamic method. In this second approach, the rotating bioreactor was used, where the fabric was placed on the roller and inside the medium containing CS (0.25–0.75%) and rotated for 5 days at 25 rpm and 30 °C. This solution proved to be more successful, allowing to overcome the problems associated with the negative influence of CS activity on the effectiveness of the nanocellulose production by the bacterial culture. The microstructure of the samples was studied using field emission scanning electron microscopy (FE-SEM), while the composition was investigated using thermogravimetric analysis, elemental analysis, and FTIR-ATR. The obtained CS/BNC hydrogel coating formed on the cotton fabric had preserved fibrillated nanostructure of BNC, increased tensile strength, and the ability to absorb and retain water. It also showed significant bacteriostatic activity. No visible bacteriocidal effect was, however, registered. The proposed methodology seems to be a promising approach to introducing various polymeric components or even nanoparticulate systems into BNC structure.

An alternative approach was presented by Wiegand et al. [135] who introduced macromolecular antimicrobial compounds into the already fabricated BNC sheets by simple incubation in the respective solutions under constant shaking at 70 rpm and in constant temperature (20 °C). Two polymeric antiseptics were compared: povidone iodine (PI) – a complex of polyvinylpyrrolidone (povidone), hydrogen iodide, and elemental iodine – and polyhexamethylene biguanide (PHMB). Although both active agents were effectively released for over 24 h (PHMB) or 48 h (PI), the analyses performed showed much more pronounced influence of PI over PHMB on the BNC structure and properties. Based on scanning electron microscopy (equipped with energy-dispersive X-ray spectroscopy, EDX), PI incorporation into the BNC fibrillary network resulted in the formation of the inhomogeneous structure composed of highly dense large regions where PI was located and significantly loosen polymeric network similar to native BNC in-between. PHMB, on the other hand, was distributed within the BNC network regularly, forming more dense, but uniform structure (see Fig. 1).

As a result, PI-enriched BNC had worse mechanical properties (compression and tensile strength measured using Universal Testing Machine TIRAtest 2710), the PI release was slow, and the found LC50/IC50 value was considerably lower. LC50/IC50 ratio (where LC50 is the half maximal lethal concentration and IC50 is the half maximal inhibitory concentration) is crucial for antimicrobials, as the higher is this value, the higher the antibacterial efficacy of material can be achieved without negatively affecting the cell viability and thus safety of application.

Authors have also compared two different BNC materials – one obtained by static method as small plates and another formed as a result of more sophisticated production process in Horizontal Lift Reactor (HoLiR). The latter method is based on the semicontinuous cultivation and was described in detail elsewhere [136]. Planar BNC fleeces or foils obtained using HoLiR were then cut (see Fig. 4). It was revealed that neither the structure of the material was significantly different for the two methods mentioned above nor was the introduction or release of the antiseptics influenced by either type or size of the BNC sample. The key role in the material structure and performance can be thus attributed to the choice of the active agent.

The fact that BNC is highly biocompatible and can be fabricated in various shapes and sizes [137] makes it a material of choice for scaffolds used in tissue regeneration. Its low affinity for cell attachment is, however, a huge disadvantage, as this property is obviously crucial for a scaffold. To increase cell attachment to BNC, its modifications with various cell adhesion proteins were assessed. Bodin et al. [138] modified the surface of BNC by adsorbing xyloglucan-bearing RGD (Arg-Gly-Asp) peptide sequence (xyloglucan-RGD, XG-RGD). RGD is the shortest fragment of the active site of various adhesion proteins and thus is widely used to increase cell adhesion of surfaces. RGD was bound covalently to xyloglucan activated by conversion to the corresponding1-deoxy-1-aminosuccinamate derivative. The surface of the modified BNC was characterized by SEM, confocal microscopy (using xyloglucan labeled with fluorescein isothiocyanate, XG-FITC), and contact angle measurements. It was shown that, due to the fact that modification was conducted in aqueous media, the structure of BNC was not significantly altered and XG-RGD was homogeneously distributed in the BNC network. A decrease in the contact angle after modification was, according to the authors, due to an increase of the number of the available hydroxyl groups. The cell adhesion studies have confirmed a positive role of RGD present on the surface of BNC on its affinity toward cells. Unfortunately, the stability of the material in physiological conditions was not verified.

As a solution to possible instability of the previous system due to desorption, Kuzmenko et al. [139] applied 1-cyano-4-dimethylaminopyridinum tetrafluoroborate (CDAP) as an activating agent for bioconjugation of adhesion proteins present in extracellular matrix to BNC. Although there are many possible activators which were previously used for cellulose, e.g., carbonyldiimidazole [140], *N*-hydroxysuccinimide esters [141], or tosyl chloride [142], CDAP seems the most promising, as it is stable to hydrolysis in a wide range of pH values allowing the direct activation in water, when –OH groups of BNC are more available due to the swelling process. After initial activation with CDAP, BNC was bioconjugated with fibronectin and collagen. XPS was used to verify the success of binding of the

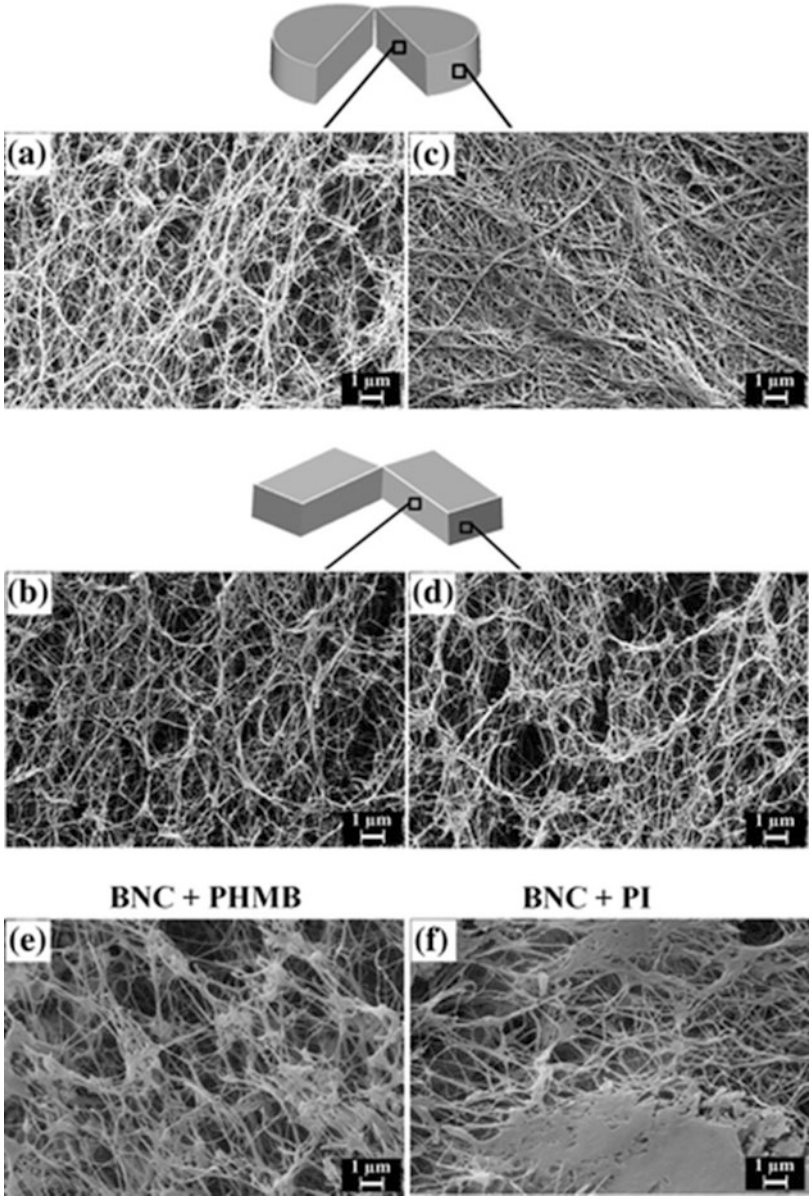

Fig. 4 SEM images of the cross section of pBNC (**a**) and cBNC (**b**) as well as of the surface structure of the side wall of pBNC (**c**) and cBNC (**d**) samples before loading. Schematic drawings represent two halves of a cylindrical pBNC sample and a cBNC cuboid. The *black frame* indicates the area (cross section and surface) where the image was taken. Micrographs of pBNC cross sections after loading of PHMB (**e**) and PVP-iodine (**f**), magnification of × 3000, and work distance of 10 mm apply to all images presented. (Reprinted from Ref. [135] with permission of Springer)

proteins. Since untreated, purified BNC showed no traces of nitrogen, the whole nitrogen content in the modified samples could be attributed to the protein molecules – both bound covalently and adsorbed. Based on the control samples prepared by a simple adsorption on the nonactivated BNC, authors concluded that, although both proteins adsorbed to some extent on the BNC surface, their amount on the activated material was considerably higher. BNC with covalently bound fibronectin or collagen was proved to be a far better scaffold for cell culturing than untreated material or BNC with physically adsorbed proteins. Only small number of cells was found on the surface of untreated BNC or after physical adsorption of proteins, and the cells had rounded shape, suggesting they were detaching from the surface. On the contrary, on BNC scaffold with covalently attached proteins, both cell lines tested (human umbilical vein endothelial cells (HUVEC) and mesenchymal stem cells (MSC)) were found in much larger quantities. The formation of confluent layers of healthy cells with well visible actin filaments was observed using fluorescence microscopy.

Polymer brushes were only recently grafted from BNC in order to control its swelling ability [143]. Thermoresponsive PNIPAM was grafted from the surface of wet BNC hydrogel using SI-ATRP in methanol/water medium. Such obtained functionalized BNC was shown to dry much slower than native BNC, especially at elevated temperature. Apparently, PNIPAM chains above lower critical solution temperature (32 °C for PNIPAM) become less hydrated and form a barrier for water trying to leave the BNC hydrogel. This novel approach has opened new opportunities for regulating swelling/drying properties of the BNC-based hydrogels that are important for their applications in, e.g., wound dressings.

4.3 Physical Modification of BNC Hydrogels

The properties of BNC can be modified chemically, by either covalent attachment of the active agents or physical interactions (adsorption, interpenetration of the polymeric networks, etc.) with low and high molecular weight compounds, but they can also be adjusted by physical processes. Ahrem et al. [144] presented an interesting attempt to modify the 3D microstructure of BNC in order to facilitate homogenous cell ingrowth in BNC hydrogels for its possible application as tissue engineering scaffold. Due to the specificity of the BNC hydrogel cultivation, the upper surface of the sheet tends to have a more dense architecture with small pores, which limits the accessibility of the hydrogel for cells. There are two main approaches to solve this problem: either by introduction of spacers/placeholders during BNC biosynthesis [145] or by postproduction methods, e.g., laser patterning [146]. The latter strategy was applied with the additional assumption that the superimposed porous structure should have a 3D architecture. This was achieved using a pulsed CO_2 laser system (max. 100 W, 100 kHz, pulse duration 170 μs, pulse energy max. 1 mJ, $k = 10{,}640$ nm) equipped with a suitable scanner. The final 3D BNC hydrogels were generated by perforating all sides of the previously cut cuboids. It was demonstrated that 3D perforations gave an excellent result for the cell ingrowth and allowed redifferentiation of chondrocytes while maintaining mechanical and chemical

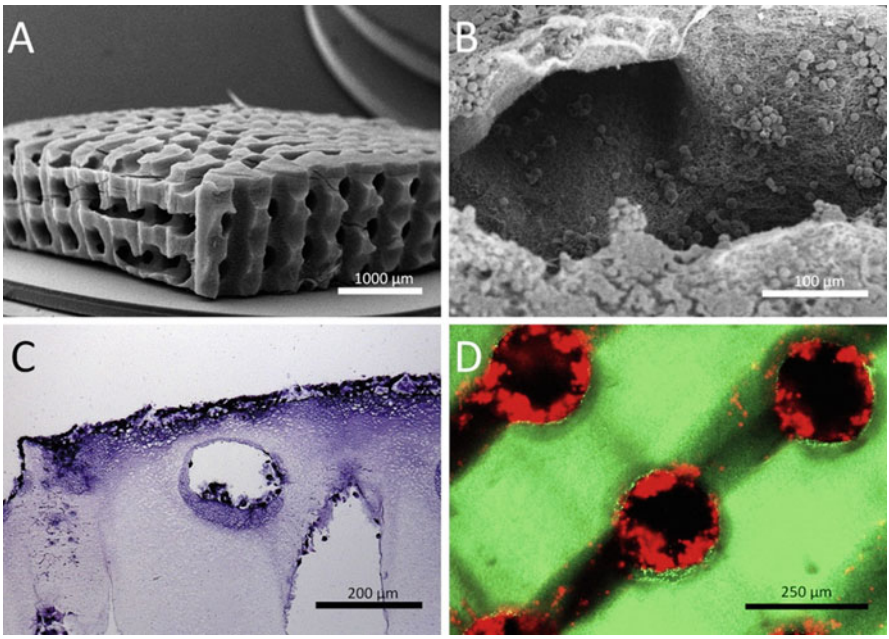

Fig. 5 Structure, cell seeding, and morphology of 3D laser-modified BNC hydrogels (LS-BNC8-3D). Scanning electron micrographs (**a**, **b**), histological cross section (**c**), and laser scanning micrograph (**d**) of 3D modified BNC hydrogels seeded with bovine chondrocytes. Overview of the 3D structure of the resulting BNC hydrogels (**a**). Side view of laser channels with bovine chondrocytes adhering to the inner surface after 24 h of in vitro culture (**b**). Seeding of BNC surface and laser channels with cells of round morphology was confirmed in histological sections (**c**) and laser scanning micrographs (**d**). Prior to cell seeding, BNC was stained with DTAF (5-((4,6-dichlorotriazin-2-yl)amino)fluorescein hydrochloride); cells were labeled with CellTracker Orange CMRA. (Reprinted from Ref. [144] with permission from Elsevier)

properties of the starting material. Figure 5 presents the summarized results of SEM, histological, and laser scanning micrography studies. Seeding bovine chondrocytes on the 3D perforated BNC resulted in colonization of the BNC surface and the newly formed channels after 24 h (Fig. 5b). The cells are also clearly visible in histological sections (Fig. 5c) and laser scanning micrographs (stained in red; Fig. 5d). Three-dimensional perforated BNC hydrogels seem to be an excellent scaffold for bone repair, as they allow for chondrocyte ingrowth and migration, as well as for extracellular matrix formation and stabilization of cells' phenotype.

5 Conclusions

Various forms of native and modified nanocellulose have already found numerous applications especially in biomedical area that were reviewed here. Thanks to the unprecedented mechanical strength among natural polymers, nanocellulose

materials are very desired for the formation of nanocomposite hydrogels that are commonly produced via physical or chemical entrapment of the nanocrystals or nanofibers in appropriate polymeric matrices. However, in order to enhance compatibility of nanocellulose with aqueous environment or improve its dispersibility in various media, including polymers, it must be subjected to chemical modifications that preserve crystalline structure and/or fibrous form responsible for high mechanical strength of the native materials. Thus, there is a growing interest in surface functionalization of cellulose nanocrystals (CNCs), cellulose nanofibers (CNF), and bacterial nanocellulose (BNC) wet sheets using both low molecular weight compounds and polymer coatings or brushes. There are also emerging technologies that would like to take advantages of its nanostructure, relatively low cost of production, versatile functionalization, and biodegradability. Nanocellulose may be attractive for fabrication of, e.g., disposable and wearable electronics, flexible solar cells, and other optoelectronic devices as well as smart textile and packing materials. For all those applications, development of efficient surface-functionalization methods to tune mechanical, optical, or even electrical properties of the new nanocellulose-based materials will stay crucial.

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Part III

Characterization Tools and Techniques of Hydrogels

Characterization Techniques of Hydrogel and Its Applications

23

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Abstract

Over the past few decades, advances in hydrogel technologies have spurred development in the personal care products and medical, pharmaceutical, and agricultural field aspects due to their unique biocompatibility, flexible methods of synthesis, range of constituents, and desirable physical characteristics. Hydrogels are hydrophilic, three-dimensional hydrophilic polymeric networks, capable of absorbing large quantities of water, biological fluids and simulating biological tissue when they get swollen due to chemical or physical cross-linking of individual polymer chains. Hydrogels are characterized by the nature of their constituent polymers, making them synthetic, natural, or hybrid. The use of natural polymers in hydrogel synthesis is advantageous in biomedical applications due to their biodegradability and non-toxicity, whereas synthetic polymers are hydrophobic, possessing strong covalent bonds within their matrix, which allow for more durability and mechanical strength. In order to design hydrogels with the desired performance and structure, characterization of hydrogel requires different tools and techniques that includes swelling, sol-gel analysis, differential scanning calorimetry, thermal gravimetric analysis, X-ray diffraction analysis, gel permeation chromatography, atomic force microscopy, and scanning electron microscopy. In this chapter, we focused and discussed about the properties, preparation methods, characterization techniques, and their most significant and current biomedical applications of hydrogels with the patents.

Keywords

Hydrogel · Polymeric cross-linking · Biocompatibility · Swelling · Sol-gel

1 Introduction

Hydrogel is a hydrophilic, three-dimensional polymeric matrix that is capable of imbibing large quantities of water and tends to simulate biological tissues when swollen and hold a large amount of water while maintaining the structure due to chemical or physical cross-linking of individual polymer chains. Hydrogels were

first reported by Wichterle and Lím [55]. By definition, water must constitute at least 10% of the total weight (or volume) for a material to be a hydrogel. Hydrogels also possess a degree of flexibility very similar to natural tissue due to their significant water content. The hydrophilicity of the network is due to the presence of hydrophilic groups such as $-NH_2$, -COOH, -OH, $-CONH_2$, -CONH -, and $-SO_3H$ [1–3].

In the last few years, novel synthetic techniques have been used to impart desirable chemical, physical, and biological properties to biomaterials. The biomaterials have either been synthesized directly from gelatin, polysaccharides, cross-linked polyacrylamide polymers, polyelectrolyte complexes, and polymers or indirectly by chemical modification of existing structures to add desirable segments or functional groups [4]. Modern biomaterials could be composed of various components, for example, metals, ceramics, natural tissues, polymers, etc. [5, 6]. Figure 1 shows the schematic representation of stimuli-responsive hydrogel that can also be responsive in different stimuli such as temperature, light, electric field, magnetic field, pH, ionic strength, etc., which results in hydrogel changes from unswollen stage to swollen stage.

They have found dominant applications in biomedicine, for example, as encapsulation matrixes for cell cultures in three-dimensional environments, as drug delivery systems, as the stationary phase for enzyme immobilizations, as a platform for biosensors, and as a medium for regenerative tissue engineering [7]. Due to their diverse applications, hydrogels have been studied extensively, although most reports have dealt with the gels formed by polymeric molecules [8].

In order to design hydrogels with the desired performance and structure, determination and characterization of hydrogel network parameters are very significant. morphological and thermal, we have discussed some important characterization techniques physicochemical, morphological and structural, and thermal such as infrared spectroscopy, X-ray diffraction analysis, atomic force microscopy, electron microscopy, thermal gravimetric analysis, differential scanning calorimetry, etc., and the applications of hydrogels with patents were discussed.

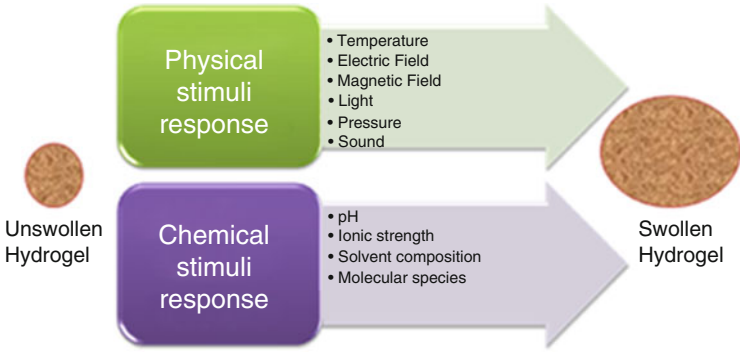

Fig. 1 Schematic representation of stimuli-responsive hydrogel

2 Preparation Methods of Hydrogel

It is well known that cross-linked networks of hydrogels are fabricated with various techniques including chemical cross-linking, physical cross-linking, grafting polymerization, and radiation cross-linking. In most cases, it seems that cross-linked agents must be present in order to avoid dissolution of the hydrophilic polymer chain in aqueous solution.

On the nature of the links, electrostatic interactions, hydrogen bonding, donor- acceptor, van der Waals forces, or even metal-ion coordination can be described for the association of polymer-polymer, polymer-drug, or polymer-bioactive components [9]. Moreover, the physicochemical properties of hydrogels such as mesh size, shape, swelling, and the permeability characteristics of the gel for various applications depend on the extension of these bonds.

2.1 Physical Methods

One of the major disadvantages of synthetic polymers is the usage of cross-linking agents in their structure, which must be removed before application due to how these agents affect the integrity of substances to be entrapped (e.g., cell, proteins, etc.) as well as their toxicity properties [10] Physically cross-linking keeps a network gel by the formation of noncovalent cross-links. Hence, there is no need to use the toxic cross-linker. Especially, physically cross-linked gels have been attracted due to relative ease of production, and also this kind of gel exhibits a reversible sol-gel transition depending on temperature, contributing to a large extent to the development of these materials for biomedical and pharmaceutical applications. The mechanical strength of physically cross-linked gels is generally low, and this kind of gels deforms easily under stress without regaining their former shape [11].

2.2 Chemical Methods

The physical hydrogels are formed by secondary interactions (such as hydrogen bonds, ionic bonds, hydrophobic interactions, crystallites, etc.); chemical hydrogels consist of irreversible covalently cross-linked network. Chemical cross-linking is a direct reaction between linear polymer or branches and at least a bifunctional component with small molecular weight called a cross-linking agent or cross-linker. This component links the polymer chains with its functional groups such as -OH, -COOH, and $-NH_2$. The overall properties, preparation, and responsive behavior of hydrogel were shown in Fig. 2.

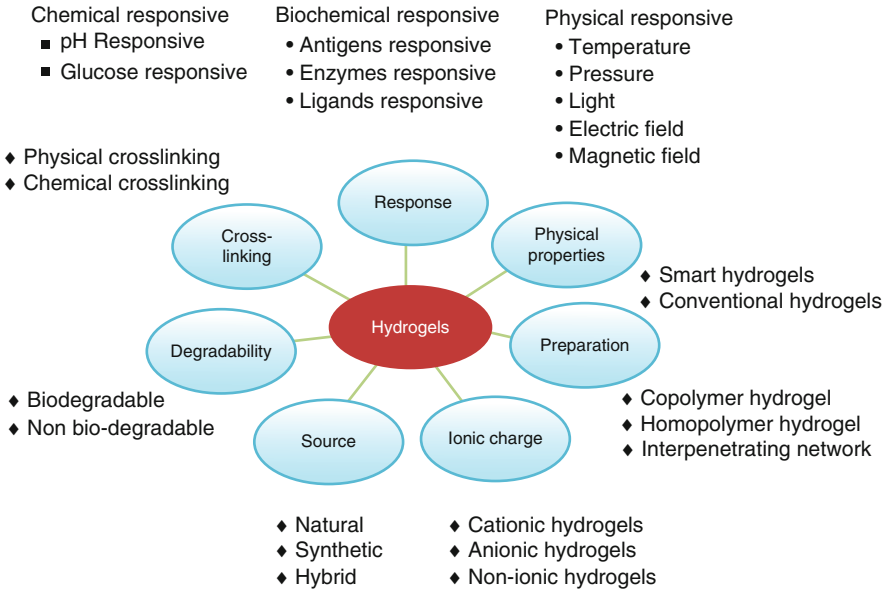

Fig. 2 Overall properties, preparation, and responsive behavior of hydrogel

3 Physicochemical Characterization

In order to design hydrogel with the desired performance and structure, determination and characterization of hydrogel network parameters are of great significance. The common techniques discussed below were chosen from a larger body of methods that provide an insight into the structure of the hydrogels. An easy way to quantify the presence of hydrogel in a system is to disperse the polymer in water using a cylindrical vial and visually observe the formation of insoluble material. Visual monitoring of the solution viscosity by turning the Universal vial upside down can also provide quick measure of the bulk viscosity. In Fig. 3 the flowchart of the physicochemical characterization tools of hydrogel such as infrared spectroscopy, X-ray diffraction analysis, atomic force microscopy, electron microscopy, and many other techniques has been described to characterize the hydrogel structure.

3.1 Solubility

Solubility can be determined by the hydrogel content of the given material that is estimated by measuring its insoluble part in dried sample after immersion in deionized water for 16 h or 48 h at room temperature [12]. Typically, 1% of the dilute concentration of the sample should be prepared to ensure that the hydrogel material is fully dispersed in water. The gel fraction is then measured as follows:

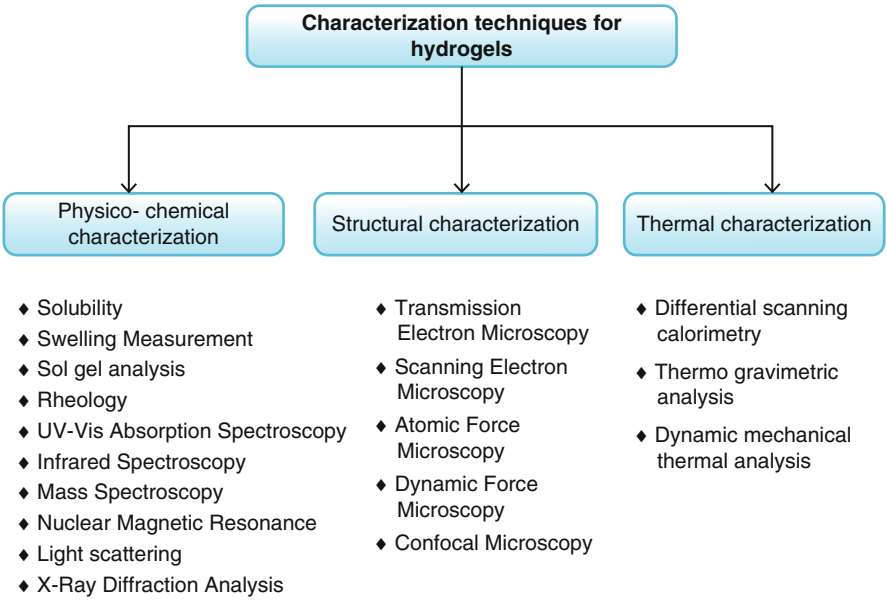

Fig. 3 Flowchart of the physicochemical characterization tools of hydrogel

$$\text{Hydrogel } (\%) = \left(\frac{W_d}{W_i}\right) * 100 \tag{1}$$

whereas W_i is the initial weight of dried sample and W_d is the weight of the dried insoluble sample after extraction with water.

In another method the accurate measurement of the insoluble sample can be determined by measuring the weight retained after vacuum filtration. Although hydrocolloids, which modifies the solvent from mild alkaline to water by following the method according to JECFA (Joint Expert Committee on Food Additives) [12]. The weight (W_1) of a 70 mm glass fiber paper (pore size 1.2 micron) is determined by drying at 105 °C for 1 h and continuously cooling in a desiccator containing silica gel. Depending on the test material, 12 wt% (S) dispersion can be prepared in distilled water followed by overnight hydration at 37 °C. The hydrated dispersion is then filtered after centrifugation for 25 min at 2500 rpm. Filter paper is dried in an oven at 105 °C followed by cooling to a constant weight (W_2) %. Insoluble fraction can be calculated as:

$$\text{Hydrogel } (\%) = \left(\frac{W_{2-}W_1}{S}\right) * 100 \tag{2}$$

Different mesh sizes can be also used depending upon the testing material. For example, to determine the gel fraction, 20-mesh steel screen (1041 μm) can be used [13].

3.2 Swelling Measurement

3.2.1 Method X

Swelling of the hydrogels can be measured by the Japanese Industrial Standard K8150 method. According to this method, the dry hydrogel is immersed in deionized water for 48 h and maintained at room temperature on a roller mixer. Once the hydrogel reaches the swollen state, it can be filtered by a stainless steel net of 30 meshes (681 μm). The swelling is calculated as follows [14]:

$$\text{Swelling} = \left(\frac{W_{s-}W_d}{W_d}\right) \tag{3}$$

where W_s is the weight of the hydrogel in swollen state and W_d is the weight of hydrogel in the dried state. The term "swelling ratio" [15] has been used for more or less comparable measurements.

3.2.2 Method Y

In an another method to measure the swelling of hydrogel, in a volumetric vial (Universal), the dry hydrogel (0.05–0.1 g) was dispersed in high quantity of water (25–30 ml) for 48 h at room temperature. Then the mixture is centrifuged to obtain the layers of water-bound material and free unabsorbed water. The free unabsorbed water is removed, and the swelling can be measured according to the Method X and following the Eq. 3.

3.2.3 Method Z

Swelling of the hydrogel can be measured according to the Japanese Industrial Standard (JIS) K7223. The dry gel is immersed in deionized water for 16 h maintained at room temperature. After swelling, the hydrogel was filtered using a stainless steel net of 100 meshes (149 μm). Swelling is calculated as follows [16]:

$$\text{Swelling} = \frac{Z}{Y} * 100 \tag{4}$$

where Z is the weight of the hydrogel obtained after drying and Y is the weight of the insoluble fraction after extraction with water.

3.3 Sol-Gel Analysis

For radiation cross-linking, the sol-gel analysis is an important characterization to estimate the parameters such as yield of cross-linking and degradation, gelation dose, etc. and to correlate these with some physicochemical properties. According to Charlesby-Pinner equation, the relation of sol fraction and absorbed dose is given in Eq. (5). This equation is widely estimated for the linear polymers like carboxymethyl cellulose [17].

$$S + \sqrt{S} = \frac{P_0}{q_0} + \frac{2}{q_0 \mu_{2,0} D} \tag{5}$$

whereas S is the sol fraction ($S = 1$gel fraction). P_0 is the degradation density, the average number of main chain scissions per monomer unit and per unit dose. q_0 is the cross-linking density, the proportion of monomer units cross-linked per unit dose. $\mu_{2,0}$ is the initial average weight of polymerization, and D is the radiation dose. Inaccuracy results can be avoided by the Charlesby-Rosiak equation (Eq. 6). This equation allows for estimation of radiation parameters of linear polymers of initial weight distribution; it is also applicable to systems when an initial material is a monomer [18].

$$S + \sqrt{S} = \frac{P_0}{q_0} + \left(2 - \frac{p_0}{q_0}\right) \frac{D_v + D_g}{D_v + D} \tag{6}$$

D is the absorbed dose in Gy. D_g is the gelation dose (a dose when the first insoluble gel appears). D_v is the virtual dose (a dose essential to change the distribution of molecular weight of the certain polymer in such a way that the relationship between the average weight and average molecular weight would be equal to 2). Though there is a limitation in Charlesby-Pinner equation that it never enhances the chain reaction that occurs during the event of ionizing radiation into its consideration and most of the experimental data of radiation polymerization do not follow this equation, it has recently shown that chain reactions, rather than polydispersity and structure, explain most of the deviations from ideal Charlesby-Pinner behavior of irradiated polymers [19]. Gelation dose can be obtained by following the equations:

$$G(x) = \frac{4.8 * 10^5}{M_{w,0} * D_g} \tag{7}$$

$$\frac{G(s)}{G(x)} = \frac{2P_0}{q_0} \tag{8}$$

whereas $G(x)$ and $G(s)$ are radiation yield of cross-linking and of scission in mol J1, respectively. $M_{w,0}$ is the average molecular weights of initial polymer before irradiation. The above equations are valid for polymers with initial and most probably molecular weight distribution and degree of polydispersity $M_{w,0} = 2$ [20]. Thus, the degradation process occurs in a polymer solution when it is subjected to irradiation; the yield of scission (mol/J) can be calculated as:

$$G(s) = \frac{2c}{Dd}\left(\frac{1}{M_w} - \frac{1}{M_{w,0}}\right) \tag{9}$$

Here, "c" is the concentration of polymer in the solution (g/dm^3); D is the absorbed dose (Gy); d is the solution density (kg/dm^3); $M_{w,0}$ and M_w are the average

molecular weight of polymer before and after irradiation, respectively. Degradation rate in irradiation is the first-order reaction, and the rate constants k can be determined by following the first-order kinetic equation [21]:

$$\frac{1}{M_t} = \frac{1}{M_0} + \frac{kt}{m} \tag{10}$$

whereas M_0 and M_t are the average molecular weight before and after the treatment for t hours, respectively, m is the molecular weight of the polymer monomer unit, and k (h1) is the rate constant.

3.4 Rheology

The aim of rheology is to establish relationship between deformation or flow and applied stress. Rheometers are operated either in a constant stress or constant shear mode. There are different types of rheometers including the Couette type (for which a "bob" rotates inside a fixed cylindrical cup full of samples), the cone-and-plate type (where a solid cone rotates on top of a flat horizontal surface), the Poiseuille type (where the fluid is kept flowing continuously between two fixed confining surfaces), the plate-and-plate type (where shear is applied to a reciprocating plate, while the second plate is kept stable), etc.

The rheological study is relatively dependent on the structural types such as association, entanglement, and cross-links present in the system. Polymer solutions are effectively viscous at low frequencies, tending to fit the scaling laws: $G' \sim \omega 2$ and $G'' \sim \omega$. Even at high frequencies, elasticity dominates ($G' > G''$). This is due to the Maxwell-type behavior with a single relaxation time that may be determined from the crossover point, and this relaxation time increases with concentration.

For cross-linked microgel dispersions, it exhibits G' and G'' being more or less independent of oscillation frequency [22]. This technique has been widely used to characterize the network structure in seroglucan/borax hydrogel, chitosan-based cationic hydrogels, and a wide range of other hydrocolloids [23].

3.5 Ultraviolet-Visible Absorption Spectroscopy

The absorption of light in the UV-Vis spectrum is an effective spectroscopic method for detecting specific chemical bonds in small molecules and in polymers. The UV-Vis absorption spectrophotometer instrument uses a Xenon pulse lamp which provides a wide wavelength range (from 190 to 1100 nm) and a dual silicon diode detector. A holographic grating is used to scan the wavelength. Absorption depends on three factors: the sample thickness t, the solute concentration c, and the absorption coefficient a. The Beer-Lambert expression relates the transmitted intensity to these

factors as $I = I_0 \exp(-a.\ c.\ t)$. The UV-Vis absorption spectroscopy method is used extensively to detect the presence and relative amount of polymers [24].

3.6 Infrared Spectroscopy

Infrared spectroscopy is the most widely used technique for identifying the chemical structure of polymers that is used to measure the vibrational energy transitions, yielding information about the different types of chemical bonds, the atoms involved, and the local chemical environment present within a material. This technique has many advantages, especially flexibility in terms of sampling methods [25]. The measurement mode is selected depending on the types of sample.

The most common sampling methods include transmission (semi-thin films and general analysis of chemical compounds), reflection-absorption (extremely thin films on metal samples), external reflection (thin films on reflecting materials), internal reflection (thick, soft materials and thin films prepared on such substrates and "wet" measurements), and diffuse reflection (powders and poorly reflecting materials) [25].

3.7 Mass Spectroscopy

Mass spectroscopy is an analytical method used to identify the composition of the polymer based on its mass-to-charge ratio of the charged particles. Chemical fragments of the sample are produced through bombardment from an ion source. They get accelerated using an electric field and passed through a magnetic field that curves their trajectory; the heavier the fragment, a larger trajectory radius it exhibits. The abundance of the various fragments was determined. In Fig. 4 an image of the mass spectroscopy instrument was shown.

Fig. 4 Image of the mass spectroscopy instrument

Matrix-assisted laser desorption/ionization (MALDI) is a soft ionization technique helpful to achieve high-resolution mass spectroscopy for synthetic and biological macromolecules as well as polymers. Instead of an ion source, the ionization is produced by the laser beam. A matrix is used to protect the polymers from being destroyed by the direct laser and to facilitate vaporization and ionization.

3.8 Nuclear Magnetic Resonance

Nuclear magnetic resonance (NMR) is a common technique for the investigation of polymers and hydrogels. Various modes of NMR (H-NMR, C-NMR, and pulsed field gradient NMR) were applied to investigate the hydrogels. H-NMR measurements were used to identify functional groups of monomer and copolymer composition for the determination of final double-bond transition at the end of the polymerization. The completion of the polymerization process and its mechanism can also be verified by H-NMR spectroscopy. The proton NMR gives information about the exchange of water molecules between the free and bound states, and it is sensitive to environments around hydrogen atoms. On the other hand, the pulsed field gradient NMR spectroscopy is a valuable tool for the characterization of hydrogel-based drug delivery systems. C-NMR is less sensitive but it has a larger chemical shift range in the hydrogel. A typical analysis of C-NMR spectrum provides expected matching chemical shifts in the cellulose [26].

3.9 Dynamic Light Scattering

Dynamic light scattering (DLS) is one of the widely used techniques to determine the particle size, molecular distribution, and parameters of a polymeric system. Figure 5 shows the dynamic light scattering instrument which is widely used for the

Fig. 5 Photographic image of the dynamic light scattering instrument

determination of molecular weight of the polymer and molecular weight distribution (MWD) or polydispersity index (PDI).

In contrast, the process of cross-linking was monitored using GPC in concert with multi-angle laser light scattering (GPC-MALLS). Other hydrocolloids, such as gum arabic, gelatin, and pullulan, can be quantified by GPC-MALLS. They have demonstrated this technique from the data obtained that can be used to assess the exact amount of the hydrogel [27].

3.10 X-Ray Diffraction Analysis

Most of the polymers are amorphous in nature, but some of them were prepared by using freeze/thaw cycles that have crystalline parts in nature that are known as semicrystalline. In Fig. 6 photographic image of the X-ray diffraction analysis (XRD) instrument is given which can identify and characterize different samples including semicrystalline polymers. As soon as the sample is being irradiated with a beam of monochromatic X-rays, a part of light gets diffracted. These diffracted rays were analyzed based on angles of diffraction, and the intensity of the diffracted rays to give information about the structural makeup, % crystallinity and crystallite dimension, interplanar atomic spacing (d-spacing), orientation, and strains present in the polymer/polymer blend matrix can be determined by the XRD technique.

Gels with different "degree of crystallinity" display a contrast in mechanical and chemical properties, which are often represented as crystallinity percentage or crystalline/amorphous ratio. The degree of crystallinity can also be determined easily with the help of XRD [28].

Fig. 6 Photographic image of the X-ray diffraction analysis instrument

4 Morphological and Structural Characterization

Morphological and structural characterization is one of the most important characterizations which is helpful for the hydrogel microstructure morphologies. This characterization confirms that the prepared hydrogels have a porous structure. It verifies that these pores are the regions of water permeation and interaction sites of external stimuli with the hydrophilic group of the prepared hydrogels. Therefore, this porous structure is one of the reason for the higher swelling ratios [29].

4.1 Transmission Electron Microscopy

Electron microscopy is used to determine the morphological or microstructure of hydrogels, yielding a three-dimensional image of the structure; particularly transmission electron microscopy (TEM) is a common method often used in the analysis of gel dispersions [30]. In Fig. 7 image of the TEM instrument is shown from this technique, by which the micrographs are obtained as a visual evaluation with size, shape, and distribution of the particles. The main aspect of this technique is to directly observe the interparticle bridge formation; when compared to all other techniques, it is one of the advantages of this technique to observe the anomalous particle formation and presence of smaller particles resulting from secondary nucleation.

Thus the subjected material should be in a dry form that can be observed only in the collapsed state. Beside, these methods cannot be used for accurate measurement of the swollen gel. Moreover, swollen gel may undergo aggregation due to reduced pressure and electron beam irradiation [31].

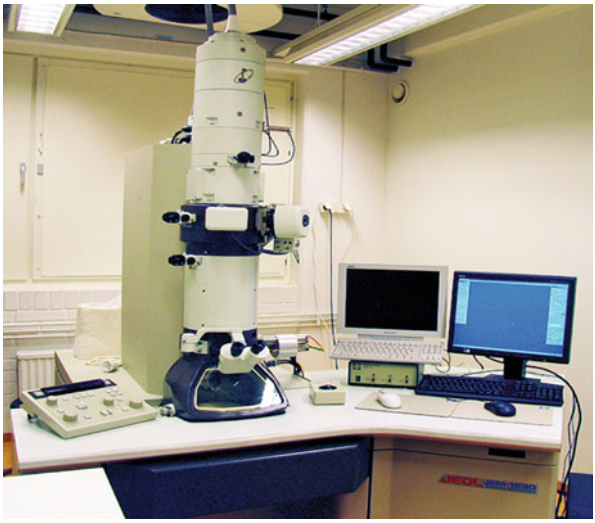

Fig. 7 Photographic image of the transmission electron microscopy instrument

Fig. 8 Photographic image of the scanning electron microscopy instrument

4.2 Scanning Electron Microscopy

Scanning electron microscopy is helpful to provide information about the surface topography, morphology, and composition of the polymer. For morphological characterization, the swollen hydrogels were freeze-dried using a freeze drier at −52 °C for 6 h. Cross sections were cut from freeze-dried film samples using a cold knife. Then the morphology of the sample was examined, and the results indicated that both swelling capacity and swelling under load were increased depending upon the increasing amount of sodium acrylate. Swelling behaviors of the hydrogel such as preliminary swelling and deswelling were also studied. The effects of pH and inorganic salt on the swelling behavior of the hydrogels were also investigated.

Magnification in SEM can be controlled up to the range of 6 orders of magnitude about 10 to 500,000 times. Figure 8 illustrates the photographic image of the scanning electron microscopy instrument which is one of the powerful tools widely used to capture the characteristic "network" structure in hydrogels [32, 33]. Moreover, it has been proved that SEM can be applied to study the network morphology [34]. SEM showed that hydrogels displayed porous surface and therefore had high surface area.

4.3 Atomic Force Microscopy (AFM)

AFM is a routine technique that can provide information about the surface properties of the hydrogel which creates a topographic image of the hydrogel surface [35]. The surface map of the materials can be generally done in two ways: either in contact profilometers or noncontact profilometers.

AFM is a contact profilometer and has the ability to capture images of nonconducting materials from a whole new horizon that explains the biomaterial can be operated either in contact mode or in tapping mode as aid to capturing the images [36]. While in the tapping mode of AFM, the tip of the cantilever has a piezoelectric element (PZTe). The cantilever gets oscillated in the resonance frequency of the

PZTe. When the tip approaches the surface of the material, this leads to an increased interaction between the surface and the tip, thereby resulting in a decrease in the amplitude of the oscillation. Once the decrease in the amplitude of oscillation is recorded and compared with an external reference, this provides information about the surface characteristics of the material. If it is in the static mode, the tip of the AFM instrument drags over the sample surface. The tip deflection of the cantilever which moves over the surface and it measures the surface properties of the sample. The deflection of the tip is routinely measured using a laser beam detector, which detects the reflected laser beam from the upper surface of the cantilever holding the tip. Nondestructivity is one of the major advantages of this method.

4.4 Dynamic Force Microscopy

Dynamic force microscopy technique displays the improved structural images of the polymer network structure after solvent extraction and its relation to the improved swelling property of the preferred system in different environmental conditions such as pH, solvent, and salt concentration. A high swelling ratio of around 600 times its dry weight is observed in water and also in low salt and solvent concentration after the methanol extraction [37].

4.5 Confocal Microscopy

Confocal microscopy uses point illumination and a spatial pinhole to eliminate out-of-focus light in samples that exhibit thicker than the focal plane. The light in the focal plane can be detected in order to improve the quality of the image. It can illuminate only one point at a time in confocal laser scanning microscopy; 2D imaging requires scanning over a regular grid in the specimen. Point-by-point images are acquired and reconstructed, allowing 3D reconstruction of complex morphologies by the software [38].

The confocal microscopy image of a semicrystalline polymer is included by dissolving poly (ethylene oxide) in ethanol which forms crystalline lamellae structure [39]. The lamellae form a spongelike morphology that allows the ethanol to be trapped in the pockets that form.

5 Thermal Characterization Techniques

Thermal characterization of hydrogels is widely practiced today in research and industry. Hydrogels are subjected to temperature-dependent structural changes during their production, processing, and application. More and more applications are being undergone with new standards, describing that hydrogels are being developed continuously. Thermal analysis technique measures the thermal transitions,

decomposition properties, and thermal conductivity (DSC, DMTA, TGA) as a function of temperature, heating rate, deformation, and atmosphere.

These techniques give insight into the specific thermal properties of the hydrogel products. They can be used to determine the composition of various compounds such as plastic and rubbers and to gain information regarding the condition or processing history of specific samples relative to the reference samples. It shows that thermal analysis is very well-suited for quality control and quality assurance. It is also important for the research and development of new materials; thermal analysis is an indispensable tool for investigating a broad range of materials properties.

Properties of thermal characterization are specific heat, thermal transitions, melting, crystallization, glass transition temperatures, degree of crystallinity, and thermal stability.

5.1 Differential Scanning Calorimetry

Differential scanning calorimetry (DSC) is a widely used technique for the characterization of the hydrogel. Image of the DSC is given in Fig. 9 which is a sensitive technique to measure the transitions of polymers as a function of varying temperatures through the changes in heat capacity and leads to the study of glass transition temperature, crystal structure, and crystal transition temperature. For the most part, this technique can be used to investigate the crystalline nature of the hydrogels; particularly the hydrogels were prepared by freezing-thawing process. Additionally, this method can be applied to determine the degrees of crystallinity and crystal size distributions of samples in the initial state (before swelling) and at different stages during swelling.

The different behaviors of water fractions in a hydrogel are most obvious in differential thermal analysis (DTA) and DSC. Upon slow heating of a frozen hydrogel (water content of around 30% or more), one often observes two

Fig. 9 Image of the differential scanning calorimetry

endothermic peaks, a sharp one corresponding to the melting of ice (~273 K) and a broader one at 10–40 K below. They are usually associated with freezable free water and freezable bound water. It should to be noted that a different explanation has also been given for the case of poly(hydroxyethyl methacrylate) (pHEMA) hydrogels: the apparent two endothermic peaks are really one peak, which is interrupted by an exothermic peak caused by amorphous ice that undergoes crystallization just below the melting transition [40].

5.2 Thermal Gravimetric Analysis

The primary thermal gravimetric analysis (TGA) thermograms were used to determine the rate of thermal decomposition reaction which was analyzed by thermal gravimetric analyzer in Fig. 10 and helpful to display parameters, such as temperature of maximum degradation (determined considering the derivative curves) and percentage of mass loss in each stage of degradation for all studied systems.

As observed, the mass loss of the hydrogel is apparently associated with adsorbed water. The effective degradation of the polymer occurs due to the high temperature about 475 °C. Once temperature increases (above 200 °C), it is typically associated with cyclic anhydride formation [41]. Moreover, at higher temperature the decomposition of anhydride rings takes place, and it is overlapped with degradation of the main chain.

5.3 Dynamic Mechanical Thermal Analysis

Dynamic mechanical thermal analysis (DMTA) allows for the quantitative determination of the mechanical properties of hydrogel under an oscillating force and as a function of temperature, time, frequency, and strain. It is a very sensitive tool for

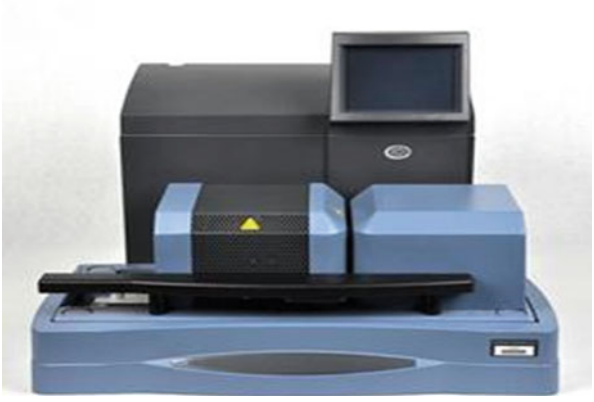

Fig. 10 Image of the thermal gravimetric analysis instrument

generating data which defines the mechanical properties of the hydrogel and composites in order to support the development of the hydrogel in industries.

It portrays linear viscoelastic properties, typically depicting a graphical plot of E' (storage modulus), E'' (loss modulus), and tanδ (loss factor) versus temperature. The DMTA is helpful to identify transition regions, such as glass transitions in plastics and resins, and may be used for quality control or product development in the temperature ranges from −180 °C to 600 °C. Special sample holder with ball-shaped pushrod in this instrument used for curing of low-viscosity liquids [42].

6 Biomedical Applications of Hydrogels

Hydrogels can absorb and retain the wound exudates, which promote fibroblast proliferation and keratinocyte migration. In addition, the tight mesh size of hydrogel structure protects the wound from infection and prevents microorganism such as bacteria and fungi to reach the wound area. However, hydrogel structure allows transporting bioactive molecules, e.g., antibiotics, and pharmaceuticals to the wound center. These molecules can be entrapped into the hydrogel network during gelling process, while these molecules can be exchanged with absorbing the wound exudates during the sustainable release process after contacting hydrogels with the wound surface. The significant tissue-like water content of hydrogel provides the needed flexibility and elasticity to adapt wounds located in different body sites [43].

6.1 Technical Features of Hydrogel for Biomedical Applications

The technical features of hydrogel are listed as follows which is suitable for biomedical applications:

- Utmost stability and constancy in a swelling environment and storage time
- Utmost absorption ability (maximum equilibrium swelling)
- Preferred rate of absorption, particle size, and porosity
- pH-neutral, colorless, odorless, and absolutely nontoxic
- Highest absorbency under load (AUL)
- Photo stability, low soluble content, residual monomer, and low price
- Rewetting capability of the hydrogel able to give back the imbibed solution or maintain it as needed (e.g., in agricultural or hygiene applications)
- Maximum biodegradability without formation of toxic groups

6.2 Hydrogels in Drug Delivery Applications

Pectin/PVP/glycine-based hydrogel membranes were developed using conventional solution casting method [44]. The swelling studies on the this hydrogel membrane

show higher swelling under simulated intestinal conditions (pH 7.4), and thermal stability of the hydrogels was found to be decreased with increase in ratio of PVP and glycine in the membranes which can be used for drug delivery and tissue engineering applications with good biocompatibility.

Enzyme-triggered method, in situ forming hydrogel of the tetronic-grafted chitosan, has been developed. In this method, tetronic was tyramine-functionalized partially and then grafted onto chitosan via the simple and organic solvent-free method [45]. Tetronic is a tetrafunctional block copolymer containing propylene oxide (PPO) and polyethylene oxide (PEO). Their hydroxyl terminal groups could be versatilely modified with some bioactive molecules or/and reactive functional groups to produce hydrogels or micelles as potential biomaterials in tissue engineering and drug delivery carriers. Polygalacturonic acid (PGA) hydrogel was synthesized using a thiol oxidation reaction [46]. This PGA film exhibits promising potential in upcoming biomedical applications including as a drug carrier for reducing early inflammatory reactions and as a physical barrier for preventing postsurgical adhesion. In Fig. 11 biomedical applications of hydrogels in various fields were given.

The smart hydrogel with shape memory was synthesized and investigated for possible biomedical science applications for specific properties such as mechanical and optical properties of the chemically cross-linked shape memory hydrogels [47]. This hydrogel was prepared from N,N-dimethyl acrylamide (DMAAm) and a crystalline monomer (i.e., stearyl acrylate (SA)) with different concentrations of DMAAm. The elastic modulus of hydrogel was dependent on the hydrophobic crystalline components, and the refractive index exhibits an inverse relationship with the degree of swelling. Due to the transparency, high refractive index, and high mechanical strength, these smart hydrogels can be used as potential material in biomedical applications.

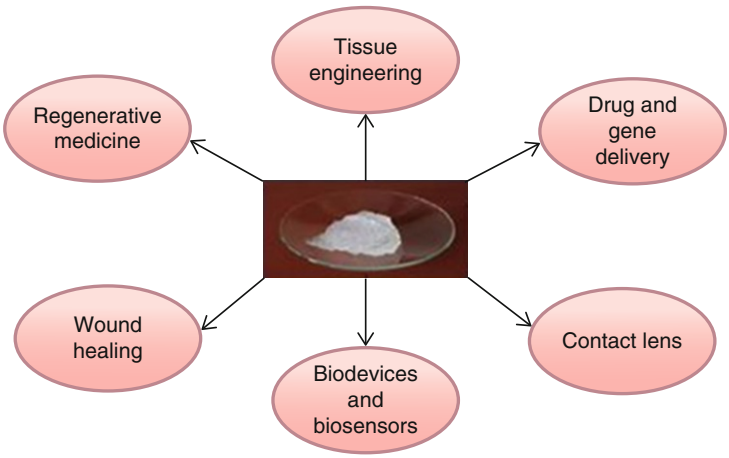

Fig. 11 Biomedical applications of hydrogel in various fields

Polyvinyl alcohol/gelatin blend hydrogel film for biomedical applications was prepared by esterification process between polyvinyl alcohol and gelatin [48]. The blend hydrogel film had sufficient strength and water-holding capacity, and its superabsorbent property could be used for various biomedical applications such as wound dressing and drug delivery systems. This cross-linked gel that exhibits superabsorbent property could be used as synthetic cartilage in synovial joints.

6.3 Magnetic Hydrogels

Synthesized magnetic hydrogels (i.e., the combination of hydrogels with micro- and/or nanomagnetic particles, e.g., gamma -Fe_2O_3, Fe_3O_4, $CoFe_2O_4$) can quickly respond to an external magnetic field (MF), enabling their enhanced controllability [49]. There are two main reasons for magnetic hydrogels for biological applications. Primarily, these magnetic scaffolds are capable of stabilizing and occupying growth factors or other biological agents bound to magnetic nanoparticles through an external magnetic field, thereby providing a nutritious environment for initial cell seeding and further cell proliferation [50, 51]. Secondly, magnetic scaffolds can respond to mechanical stimulus through interactions between magnetic nanoparticles and an alternating magnetic field (AMF), which may be employed to control cell biological behavior such as the angiogenesis process [52, 53].

Hyaluronic acid (HA), or hyaluronan, is a linear polysaccharide that consists of alternating units of a repeating disaccharide, β-1,4-D-glucuronic acid-β-1,3-*N*-acetyl-D-glucosamine. Hyaluronic acid hydrogels can also be used for biomedical applications such as cartilage tissue engineering, cardiac repair, molecule delivery, and control of stem cell behavior [54]. Additionally, HA-based hydrogels may impart biological activity to cells, as evident by changes in cellular behavior, including stem cell differentiation, when interacting with biomaterials based on HA compared to other polymers.

6.4 Hybrid Hydrogel for Biomedical Applications

Hybrid hydrogel was prepared using nanocomposites and hydrogels which developed three-dimensional (3D) GelMA hydrogels [55]. Hybrid hydrogel systems can also be formed by mixing GelMA with nanoparticles such as carbon nanotubes and graphene oxide and other polymers to form networks with desired combined properties and characteristics for specific biological applications. This hydrogel exhibits similar essential properties of native extracellular matrix (ECM) due to the presence of cell-attaching and matrix metalloproteinase, which allow cells to proliferate and spread in GelMA-based

scaffolds. Including engineering of bone, cartilage, cardiac and vascular tissues. Other applications of GelMA hydrogels include cell signaling, drug and gene delivery, and biosensing. In a recent study, the surface of titania was functionalized with amine groups to facilitate covalent interactions between the nanoparticles and carboxymethylcellulose [55]. These hybrid nanocomposite hydrogels can be used to encapsulate cells for tissue engineering applications.

7 Patents

Wichterle and Lim were the first to describe a hydrogel based on poly-2-hydroxyethyl methacrylate (PHEMA) as a synthetic biocompatible material useful for contact lens applications in 1960 [55]. In 1962, PHEMA lenses were first introduced in Europe but not succeeded. The National Patent Development Corporation (NPDC) bought the license to this technology in 1965. Later, it was sold to Bausch & Lomb, and they optimized Wichterle's spin-casting process and finally acquired the approval from the Food and Drug Administration (FDA) for their PHEMA lenses in 1971.

For cast-molding silicone hydrogel contact lenses, innovative molds were useful which have been described in the US Patent 6,861,123 B2 assigned to Johnson & Johnson Vision Care, Inc. They patented the method for polyolefin inserts in producing the molds in which these are used to make lenses [56].

In US Patent 3,679,504 [57], Wichterle proposed a method of forming colored soft contact lenses and ophthalmic prostheses. The colored ingredient was integrated between two transparent hydrogel layers bound together by polymerizing the hydrophilic monomer mixture.

In US Patent 3,575,946 [58], the use of macromonomers can potentially eliminate in the preparation of hydrogel the need for their purification as these macromonomers are often nontoxic [59]. In US Patent 4,472,327 [59], Neefe disclosed a method of making cosmetic hydrogel contact lenses that modified the apparent color of the iris by using small light-reflecting particles embedded in a colored transparent matrix. The reaction mixture may include a "silicone-containing monomer," which is described in the US Patent 3,808,178 [60].

8 Conclusion

Compared with other types of biomaterials, hydrogels have distinct properties such as high water content, controllable swelling behavior, ease of handling, as well as biocompatibility, which makes them as attractive material for biomedical

applications. Hydrogels, which are three-dimensional cross-linked polymeric networks able to swell in large amounts of water, should be considered prime candidates for carriers or matrices for cells in tissue engineering, self-healing materials, and delivery vehicles for drugs and biomolecules.

9 Future Scope

In the future, hydrogel-based carriers can be an excellent candidate for the successful administration of drugs at the desired rate and site in the body. Specific release rates and dissolution profiles could be achieved with the development of new hydrogels with different hydrophobicity/hydrophilicity and structural characteristics.

These systems could improve the delivery of more sensitive molecules and be employed in the treatment of pathologic conditions such as diabetes or even cancer. Specifically, more developments are expected in the use of hydrogels for delivery of therapeutic proteins and peptides.

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Thermal Behavior of Bacterial Cellulose-Based Hydrogels with Other Composites and Related Instrumental Analysis

24

Norhayati Pa'e, Mohd Harfiz Salehudin, Nor Diana Hassan, Aishah Mohd Marsin, and Ida Idayu Muhamad

Contents

Abstract

Hydrogel is a network of polymer chains that are hydrophilic and able to absorb and release large amount of water in a reversible manner. At present, synthetic and natural hydrogels have been extensively studied due to their responsive

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properties toward specific environmental stimuli such as pH, temperature, and ionic strength. This includes hydrogel from natural cellulose obtained by bacterial fermentation. The capability of hydrogel for transmitting and resulting in a useful response is termed as the smartness ability of the material. Studies on thermal behavior and performance allow fabrication of hydrogels that exhibit smart properties such as with temperature sensitivity or ideally dual (pH/temperature) sensitivity. The designed hydrogel can be characterized thermally using instrumental analyses, for example, the Differential Scanning Calorimetry (DSC), Dynamic Mechanical Analysis (DMA), Thermomechanical Analysis (TMA), and Thermogravimetric Analysis (TGA). These allow evaluation on the glass transition temperature, melting temperature, degree of crystallinity, and mechanical properties of the fabricated hydrogels. Furthermore, understanding thermal behavior of the hydrogels can help to elucidate the effect of the preparation technique and treatment on properties of the hydrogels. This gives advantages on producing hydrogel with required properties for defined application. In this work, thermal characterization of bacterial cellulose-based hydrogels and its composites using related instrumental analyses were discussed.

Keywords
Cellulose-based hydrogel · Smart hydrogel · Bacterial cellulose · Thermal behavior · Thermal analysis

1 Cellulose as Natural Hydrogel Material

Hydrogel, a three dimensional, hydrophilic, cross-linked polymeric network has been widely used by researchers for various applications in the form of solid tablets, capsules, films, slabs, coatings, and micelles since many years ago. It has the ability to imbibe huge amount of water or biological fluid due to the existence of hydrophilic groups such as hydroxyl, carboxyl, amino, and other groups in the polymer forming hydrogels structure [1]. These hydrogels exhibit a thermodynamic compatibility with water which allows them to swell in aqueous media where this characteristic helps the hydrogel to absorb and release water solutions in a reversible manner. Due to its high water content, porosity, and soft consistency, hydrogel closely stimulates natural living tissue, more than any other class of polymer biomaterials [2]. The hydrogel structures are mainly influenced by the classification of sources, polymeric composition, configuration, type of cross-linking, physical appearance, and network electrical charge [3].

During last two decades, natural hydrogels are gradually replaced by synthetic hydrogels which have longer service life, high capacity of water absorption, and high gel strength. Fortunately, synthetic polymers usually have well-defined structures that can be modified to yield tailorable degradability and functionality. Hydrogels can be synthesized from purely synthetic components. Also, it is stable in the conditions of sharp and strong fluctuations of temperatures.

Natural hydrogel was the first polymer form that has been used as a carrier in various food processes or in drug-delivery system. The terms "natural" shows that

the hydrogel was made from natural resources such as plants and animals. The use of natural hydrogel in variety of applications is based on its properties which possess no toxicity effect and harmless for human consumption. Natural hydrogel also exhibits important characteristics in the making of drug carrier and tissue scaffold which are biocompatible, biodegradable, and nontoxic. Polysaccharide and protein are widely studied in the making of natural hydrogel and used in oral drug-delivery application. Polysaccharide has the ability to change its structure chemically or biochemically. Furthermore, with the extraction from plant based, polysaccharide shows nontoxic, harmless, highly stable, and high compatibility properties that suits the production of high efficiency of drug carrier.

The most widely studied polysaccharide for natural hydrogels includes cellulose and its derivatives. Even though natural resources show harmless effect in various applications, natural resources could not stand alone in the production of hydrogel. Cellulose hydrogels can be prepared from a cellulose solution through physical cross-linking because cellulose has many hydroxyl groups which can form hydrogen bonding linked network easily. The addition of cross-linker or polymerization with other monomer was widely studied to form an optimum hydrogel in the production of drug carrier and tissue engineering [3]. Bacterial cellulose is also a strong candidate for the fabrication of cellulose-based hydrogels, since certain bacterial species possess the ability to create pure cellulose hydrogel.

1.1 Introduction to Cellulose

Cellulosic materials are exclusively renewable resources and abundant fibers that exist in nature. Cellulose is expected to become the main chemical resource in the future [4, 5]. Moreover, numerous new functional materials from cellulose are being developed over a broad range of applications, because of the increasing demand for environmentally friendly and biocompatible products [6]. Additionally, agricultural waste offers economically feasible cellulose sources than any other source of fibers currently in use. Those ample sources are not only renewable but they also have demand in industrial market since long time ago especially in Asian countries [7]. Yet, there are thousands of tons of agricultural waste produced without proper utilization, which found to be useful in preparing polymer composites for commercial purposes, for example, empty fruit bunches, sisal fibers, wheat straws, and others [8].

As shown in Fig. 1, cellulose is a long linear chain polymer with repeating units of D-glucose. Cellulose having abundant hydroxyl groups can be used to prepare hydrogels easily with fascinating structures and properties. Water soluble cellulose derivatives are mostly biocompatible which can be used as thickener, binding agents, emulsifiers, film formers, suspension aids, surfactants, lubricants, and stabilizers, especially as additives in food, pharmaceutical, and cosmetic industries. Selective cellulose derivatives, including methyl cellulose (MC), hydroxypropyl cellulose (HPC), hydroxypropylmethyl cellulose (HPMC), and carboxymethyl cellulose (CMC) have been used to fabricate cellulose-based hydrogels through physical cross-linking and chemical cross-linking. Therefore, there is a need to study cellulose-based hydrogels in both fundamental research and industrial application [9].

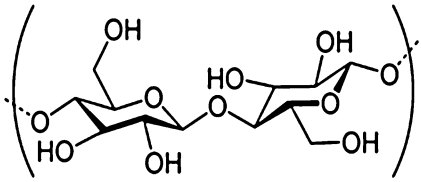

Fig. 1 Cellulose as polymer of β-D-glucose

Recently, numbers of natural cellulose and its composites have been used as hydrogel material [10–12]. Cellulose-based hydrogels have wide applications in tissue engineering [13], controllable delivery system [14], blood purification [15], sensor [16], agriculture [17], as well as water purification [18], and chromatographic supports [19]. Moreover, cellulose is environmental friendly and low-cost hydrogel material, which will form a viable substitute for petroleum-based materials in the near future.

1.2 Bacterial Cellulose as Alternative for Plant Cellulose

In recent time, bacterial cellulose has started to be used to substitute plant derived cellulose because of its excellent and promising properties [20]. Bacterial cellulose is a source of cellulose other than plant cellulose. It is produced by bacteria from many genera such as *Acetobacter, Achromobacter, Agrobacterium, and Sarcina*. However, from that list of cellulose producers, the species that is well known with its capability to produce cellulose in large quantity is *Acetobacter* genus. While within that species, *A. xylinus* or *Acetobacter xylinum* has been used extensively in research and studies [21]. *A. xylinum* produces cellulose from glucan chains that extrude into the fermentation medium from its pores. This process is repeated until a bundle of microfibrils are gathered and form the bacterial cellulose. Medium for bacterial cellulose fermentation can be obtained from any kind of carbon sources or sugars. *Acetobacter* needs oxygen to produce the bacterial cellulose. Therefore the production will occur mostly at the surface of the liquid [22–24].

1.2.1 Synthesis of Bacterial Cellulose

Bacterial cellulose has superior properties such as ultra-fine network structure, high biodegradability, and high mechanical strength as compared to plant cellulose [25]. It is expected to be a good alternative for biodegradable biopolymer. According to Lee et al. [26], cellulose synthesized by the bacteria *A. xylinum* and plant cellulose is highly crystalline. However, the arrangements of glucosyl units of the crystallites make them differ to each other.

A. xylinum is acetic acid-producing bacteria widely used as the model system to study the enzymes and genes involved in cellulose biosynthesis. This species of gram-negative bacteria has high capability to produce cellulose by converting carbon source such as glucose or sucrose to cellulose. It is well known that *A. xylinum* is an obligate aerobe and forms cellulose at the air/liquid interface in undisturbed cultures. Figure 2 demonstrates the formation of microfibrils by *A. xylinum*.

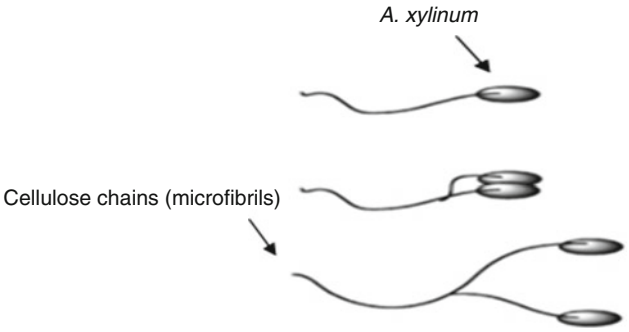

Fig. 2 Secretion of microfibrils by *Acetobacter* cells

Multiple cellulose chains or microfibrils are synthesized in the interior of bacterial cell and spun out of bacterial cellulose export component or nozzles [27]. The cellulose synthesis will continue until a limited condition such as when carbon sources are insufficient or when the bacterial cellulose filled the discs in fermentation using rotary discs reactor [28].

Most cellulose-producing acetic acid bacteria can convert glucose to gluconic acid and ketogluconic acid. The enzyme responsible for the conversion of glucose to gluconic acid is membrane bound glucose dehydrogenase (GDH) [29]. This undesirable process deviation will simply remove glucose from the fermentation medium and avoid the formation of cellulose [30].

1.2.2 Optimum Condition for Growth of *Acetobacter xylinum*

Acetobacter xylinum is found in specific environment which they can grow. It can be influenced by a variety of physical and biochemical factors. Physical factors include pH, temperature, oxygen concentration, moisture, pressure (hydrostatic and osmotic), and radiation. Meanwhile biochemical factors include availability of carbon, nitrogen, sulfur, phosphorus, traces elements, and vitamins.

Optimum pH is the pH where it can give a best condition for the growth rate of bacteria. The pH scale measures hydrogen ion (H^+) concentration. This hydrogen concentration gives an effect to the enzyme activity and thus influences the microbe growth. High pH corresponds to low concentration of H^+, while low pH corresponds to high concentration of H^+ and neutral pH is condition where number of H^+ and OH^- (hydroxyl ions) is equal. *A. xylinum* is an acidophilic bacterium. Hence it is capable to live at pH as low as 3.5 [31], however its optimum pH is 5.4–6.3 [32].

Optimal temperature is the temperature at which the growth rate of the microbe is the best. The optimal temperature for *A. xylinum* growth is between 25 °C and 30 °C. Typically organism whose optimum growth temperature is between 20 °C and 40 °C is classified as mesophylls. So *A. xylinum* is a mesophylls bacterium. At temperature 37 °C, the bacteria failed to multiply even in an optimal medium. It is because at high temperature the cell component of the microbe such as nucleic acid and protein will

be denatured. Therefore, temperature is one of the important factors that give a large impact for the microbial growth [33].

A. xylinum is an obligate aerobic bacterium that has an oxygen-based metabolism. Thus, it requires oxygen for aerobic respiration to oxidize substrates such as glucose in obtaining energy and convert the glucose into cellulose. The bacteria cell obtains oxygen at the air-liquid interface where the cellulose is produced. The oxygen supply is considered as the limiting factor for bacterial growth and cellulose formation. The oxygen concentration has a limitation; too much dissolved oxygen inside the fermentation medium will increase the level of gluconic acid but too low oxygen concentration will reduce the production of cellulose due to the insufficient oxygen source for the culture to grow [34].

Every organism must find an environment with all the substances required for energy generation and cellular biosynthesis. The chemicals and elements are utilized for nutrients to grow, repair themselves, and replicate. The elements are carbon, nitrogen, sulfur, phosphorus, and various trace elements. *A. xylinum* growth needs some major elements which are found in water, inorganic ions, small molecule, and macromolecule which serve either as structural or functional role in the cells [35].

1.2.3 Medium Used for Fermentation of Bacterial Cellulose

Bacterial cellulose can form in many medium such as coconut water, fruit juice, and domestic waste product, or in a nutrient medium. Traditionally, bacterial cellulose has been produced in static trays by using coconut water or other natural medium such as sugar cane, pineapple extract, etc. Table 1 below shows various medium used for fermentation of bacterial cellulose.

2 Bacterial Cellulose as Natural Hydrogel Material

Bacterial cellulose as a natural hydrogel is extremely hydrophilic, absorbing 60–700 times its weight in water. The nanofiber presence in a structure of multiple cellulose layers in bacterial cellulose. It is capable to hold an extensive amount of liquid between the fibrous layers to form a hydrogel [43]. Wood or cotton must be physically disintegrated to make them hydrophilic [44], compromising strength in the process. Since bacterial cellulose is formed in a hydrophilic matrix and needs no treatment, it will retain its long fibrils and exceptional strength. These properties open the doors to new applications in aqueous systems, such as replacing chemicals and dyes with water while retaining the native form and properties of the pellicle.

2.1 Properties of Bacterial Cellulose Hydrogel

The bacterial cellulose was used as hydrogel since it is pure and extremely hydrophilic. Therefore, it needs no treatment which makes its original properties retained. These unique characteristics of bacterial cellulose open many room for

Table 1 Production of bacterial cellulose using different medium

Medium	Explanations
Palm oil mill effluent (POME) [36]	– 8.0 g of sucrose, 0.8 g of yeast extract, and 0.3 g of KH_2PO_4, and 0.005 g of Mg_2SO_4 in 100% (v/v) of POME concentration – Static fermentation process at pH 5.5, temperature 26 °C, and 7 day incubations – Bacterial cellulose wet weight is 29.25 g
Pineapple waste [37]	– Optimum conditions are pH 5.50, temperature at 30 °C, and 80% of pineapple concentration – Bacterial cellulose produced is 3.43 g – Has a great potential to use as a carbon source in production of bacterial cellulose
Bacterium isolated from rotten fruit [38]	– Used different fruit like apple, pineapple, orange, sweet lime, and pomegranate – Condition used is temperature at 30 °C
Maple syrup [39]	– Fermentation in a rotary shaker with shaking speed 135 rpm, inoculum age 3 days, inoculum volume 6% (v/v) and incubation temperature 25 °C – Optimal conditions for bacterial cellulose production are: carbohydrate 30 g/l, $(NH_4)_2SO_4$ 3.3 g/l, KH_2PO_4 1 g/l, yeast extract 20 g/l, citric acid 1.6 g/l, trisodium citrate dehydrate 2.4 g/l, ethanol 0.5% (v/v), acetic acid 0.5 g/l, $MgSO_4$ 0.8 g/l
Sucrose [40]	– Shigeru Yamanaka medium (50 g sucrose, 5 g yeast extract (Bacto), 5 g ammonium sulfate, 3 g potassium dihydrogen phosphate, and 0.05 g magnesium sulfate) – Fermentation in RDR at pH 5.0 or 4 days at 28 °C produced 139.78 g wet cellulose
Agricultural waste [41]	– Used coconut and pineapple juices – Condition used are temperature at 30 °C, pH 4.75 and fermentation in 5 L fermenters – Give highest productivity when using coconut juice
Glucose, mannitol and xylose [42]	– Using a Herstin-Schramm nutrient medium containing: 2% glucose, 0.5% yeast extract, 0.5% bacto pepton, 0.115% citric acid, 0.27% Na_2HPO_4, 0.05% $MgSO_4$, 1% etanol – Added after sterilization of the base medium – Fermentation at temperature of 30 °C

new applications as the properties of bacterial cellulose can be changed by manipulating the fermentation process. The bacterial cellulose has more advantages compared to plant cellulose. The most significant advantage is its purity. The bacterial cellulose has no hemicelluloses or lignin as in plant cellulose, thus less processing step is required. Besides, its structure is stronger and finer compared to plant cellulose which is due to longer and finer fiber length of bacterial cellulose. Figure 3 shows a microstructure of bacterial cellulose and plant cellulose at 5000 times magnification.

Based on the SEM image, it can be seen that bacterial cellulose has a smooth and finer network of cellulose fibrils while plant cellulose also consists of similar fibrils but larger compared to bacterial cellulose. The bacterial cellulose grows following the surface of the vessel; therefore, it can be grown to almost any desired shape.

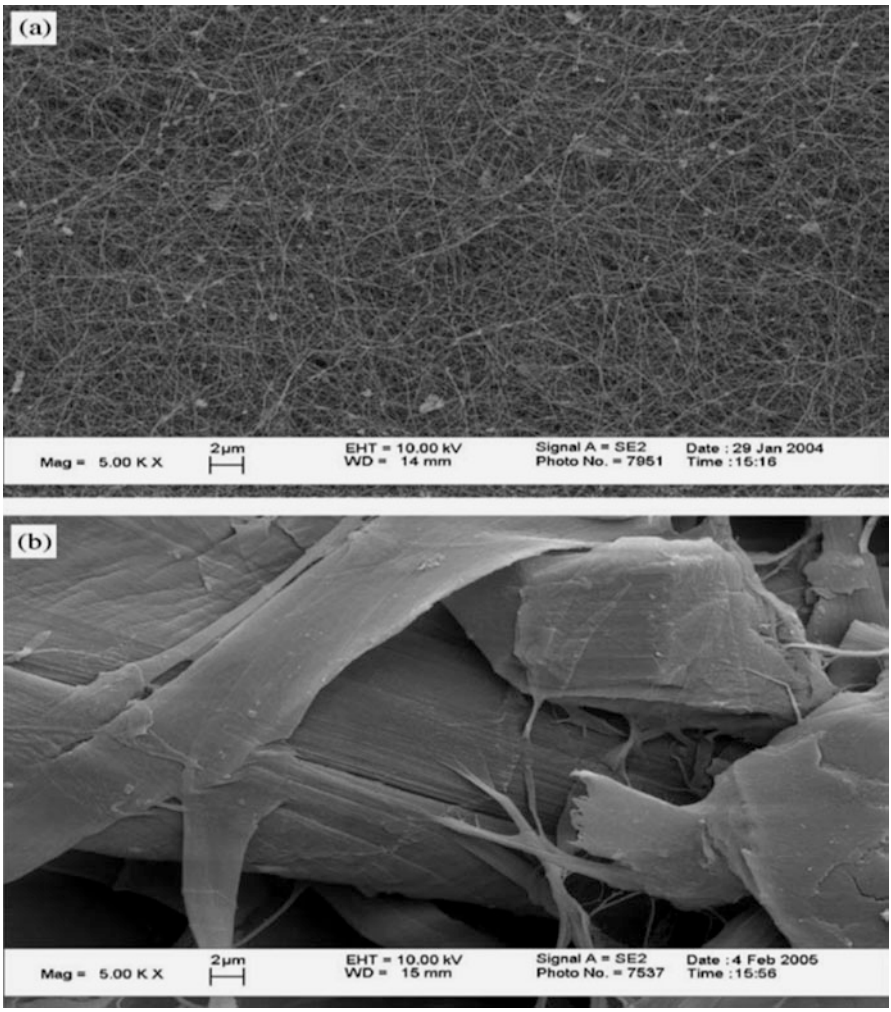

Fig. 3 SEM images of (**a**) bacterial cellulose and (**b**) plant cellulose at 5000 times magnification

Besides, it can be produced using variety of carbon sources as the fermentation substrate [45].

Cellulose produced by *A. xylinum* is markedly different than cellulose obtained from trees and cotton with many advantages that can be commercially useful. Bacterial cellulose is devoid of lignin and hemicellulose, extremely hydrophilic, and has excellent shape and strength retention. It can be produced from many different substrates, its properties can be altered, and it can be made into just about any shape or size in the reactor vessel.

Cellulose made from trees must undergo many stages of pulping process to remove lignin and other compounds. This step is costly but necessary for paper

manufacturing. Bacterial cellulose is pure and does not have to endure harsh processing. Fewer steps are required to process bacterial cellulose, hence the cost is cheaper and less waste is generated. But a big advantage is that the cellulose fibers remain intact because of the simpler processing, and thus the cellulose remains stronger and retains its attractive properties.

Bacterial cellulose pellicle is extremely hydrophilic, absorbing 60–700 times its weight in water. Wood or cotton must be physically disintegrated to make them hydrophilic [44], compromising strength in the process. Since bacterial cellulose is formed in a hydrophilic matrix and needs no treatment, it will retain its long fibrils and exceptional strength. These properties open the doors to new applications in aqueous systems, such as exchanging chemicals and dyes with the water while retaining the native form and properties of the pellicle.

Bacterial cellulose can be produced using a variety of substrates, with different strains showing preference for certain ones. This is important for commercial applications as inexpensive substrates decrease the costs. By adding certain substrates or by manipulating the operating conditions, it is possible to change the properties of the cellulose. For instance, the addition of carboxymethyl cellulose (CMC) during cellulose formation increases the water holding capacity to 1000 times its dry weight. The ability to alter the cellulose as it is formed rather than through subsequent processing saves money and maintains the structural properties of the virgin pellicle.

Several researchers have shown the ability to produce cellulose in a predetermined shape. Since the cellulose forms at the air/liquid interface, the shape of the interface will determine the shape of the pellicle. White and Brown [46] were able to form a seamless cellulose glove using gas permeable mold submerged in an *A. xylinum* culture. The cells congregated around the mold and formed cellulose. This can be done in situ to achieve any desired shape.

2.2 Application of Bacterial Cellulose Hydrogel

Bacterial cellulose has similar chemical structure as plant cellulose, but it has higher purity without lignin or hemicelluloses. Therefore, using bacterial cellulose is more economic compared to plant cellulose because we can skip many stages in the production of pure plant cellulose [21] thus lower the production cost. Moreover, its distinguished properties such as ultrafine nanofiber, biodegradability, and high mechanical test [47] make it a promising material for many applications.

The interest on applications of bacterial cellulose grows rapidly since 1990s. Those applications started with the use of pure bacterial cellulose and expand to bacterial cellulose composites via the modification of bacterial cellulose using other materials. Table 2 shows some patented applications of bacterial cellulose in different fields.

Table 2 Applications of bacterial cellulose hydrogel

Material	Applications	Patent
Bacterial cellulose- poly (2 – hydroxyethyl methacrylate)	Contact lenses and optic component for biosensor	US20130011385 A1 [48]
Bacterial cellulose hydrogel	Cold pack	CN 201806818 U [49]
Bacterial cellulose nanosilver	Mask	CN 101589854 B [50]
Poly(vinyl alcohol)- bacterial cellulose	Soft tissue replacement, medical devices, artificial dura mater	CN101053674 A [51] US 20050037082 A1 [52]
Gelatinous bacterial cellulose	Production of soft and light fibers	US 5962676 [53]
Reticulated bacterial cellulose	Replacement for latex binders	US 4919753A [54]

3 Thermal Behavior of Bacterial Cellulose Hydrogel and Related Instrumental Analysis

Bacterial cellulose and its composites can be characterized in many different ways. These important properties will vary from application to application. Rapid development on hydrogel researches put hydrogels in situations that challenge the thresholds of their thermal capabilities. For example, the use of stimuli-responsive hydrogels, also known as smart hydrogels, are cross-linked polymeric materials that show drastic changes in their swelling ratio with the changes of the external environment, e.g., pH [55] and temperature [56]. These smart hydrogels have been developed for various applications, such as tissue engineering [57], immobilization of enzyme [58], and drug delivery [59]. It is therefore important to understand its behavior under the influence of thermal loads using thermal analysis.

3.1 Introduction to Thermal Analysis

Thermal analysis is a branch of material science where the properties of materials are studied as they change with temperature. Sometimes, it is crucial to maintain the conditions of a process under control. This requires some analysis to be done regarding the materials and environment that are used in the process. For instant, each material should never go above some certain temperature or its components will degrade which resulted to malfunction.

Thermal analysis techniques provide a variety of important information of use to the researcher. Several methods are commonly used such as thermogravimetric analysis (TGA), differential scanning calorimetry (DSC), thermomechanical

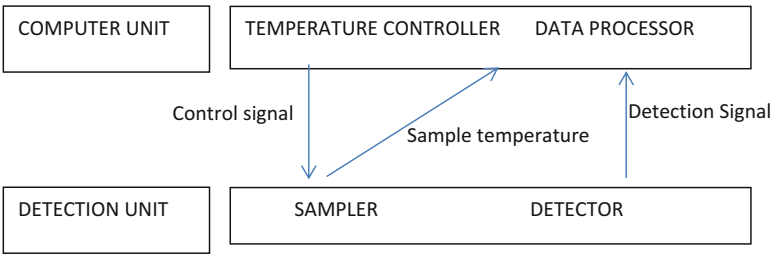

Fig. 4 Basic configuration of thermal analyzer

analysis (TMA), and dynamic mechanical analysis (DMA). Figure 4 shows the basic configuration of thermal analysis instrument which includes computer unit and detection unit.

The Detection Unit comprises of furnace, sample holder, and temperature sensor for detection of the sample temperature and property. Meanwhile, the computer unit includes temperature controller and data recording unit for controlling the furnace temperature and records the signals. Temperature control, data recording, and analysis are all computer-controlled. The combination of the furnace and sensor enables the various types of the measurement techniques. This computer can be connected to the several instruments which have the other types of measurement techniques, which enable the simultaneous measurement and analysis. Table 3 listed the thermal analysis instrument and the properties measured by each technique.

The importance of thermal analysis in the manufacture of hydrogel can be seen in terms of processing, storage, and application. For example, thermal analysis helps in determining the appropriate processing temperature for the production of hydrogel with the desired characteristics. Additionally, the information from this thermal analysis allows hydrogel storage to be carried out at the appropriate temperature to avoid degradation of the products and at the same time can prolong the shelf life.

3.2 Thermogravimetric Analysis (TGA)

3.2.1 Introduction to Thermogravimetric Analysis

Thermogravimetric Analysis is a technique to characterize materials used in various environmental, food, pharmaceutical, and petrochemical applications. In TGA, the mass (weight increases or decreases) of a substance is monitored as a function of temperature or time. Changes in physical and chemical properties of materials are measured as a function of increasing temperature (with constant heating rate) or as a function of time (with constant temperature and/or constant mass loss).

TGA can provide information about physical phenomena, such as vaporization, sublimation, absorption, and desorption. Likewise, TGA can provide information about chemical phenomena including chemisorption, dehydration, decomposition, and solid-gas reactions (oxidation or reduction).

Table 3 Thermal instrumental analysis and properties measured

Technique	Property
Thermogravimetric analysis	Mass changes, dehydration, decomposition, oxidation, reduction
Differential scanning calorimetry	Melting, glass transition, the crystallization, specific heat capacity
Thermomechanical analysis	Thermal expansion, the thermal shrinkage, the glass transition, curing reaction
Dynamic mechanical analysis	Relaxation, the crystallization, and the curing reaction

TGA is commonly used to determine selected characteristics of materials that exhibit either mass loss or gain due to decomposition, oxidation, or loss of volatiles (such as moisture). Common applications of TGA are:

1. Materials characterization through analysis of characteristic decomposition patterns.
2. Studies of degradation mechanisms and reaction kinetics.
3. Determination of organic content in a sample.
4. Determination of inorganic (e.g., ash) content in a sample, which may be useful for corroborating predicted material structures or simply used as a chemical analysis.

TGA relies on a high degree of precision in three measurements: mass change, temperature, and temperature change. Figure 5 shows image of TG analyzer and its schematic diagram. It consists of a sample pan that is supported by a precision

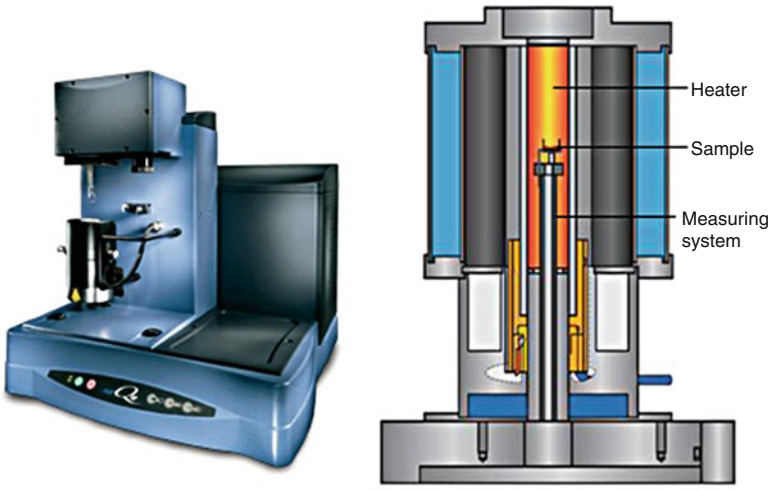

Fig. 5 Thermogravimetric Analyzer and its schematic diagram

balance. That pan resides in a programmable furnace which can be heated or cooled during the experiment. The furnace can be programmed either for a constant heating rate or for heating to acquire a constant mass loss with time. The mass of the sample is monitored during the experiment.

The TGA instrument continuously weighs a sample as it is heated. As the temperature increases, various components of the sample are decomposed and the weight percentage of each resulting mass change can be measured. Results are plotted with temperature on the X-axis and mass loss on the Y-axis. The data can be adjusted using curve smoothing and first derivatives are often also plotted to determine points of inflection for more in-depth interpretations.

TGA can be utilized for the analysis of the thermal decomposition, the oxidization, the dehydration, the heat resistance, and kinetics analysis. By combining with the other measurement technique, variety of information can be achieved from one sample. In particular, TG/DTA simultaneous measurement instrument is the most common.

3.2.2 Characterization of Bacterial Cellulose Hydrogel Using TGA

In bacterial cellulose characterization, TGA was usually conducted to determine its thermal degradation based on mass loss recorded. Figure 6 shows sample of TGA curve of bacterial cellulose. Basically, the change in the weight loss can be categorized into two different regions. From room temperature to 200 °C, the weight loss was owed to water and solvent evaporation. From 200 °C to 500 °C, the change in the weight loss was due to organic decomposition.

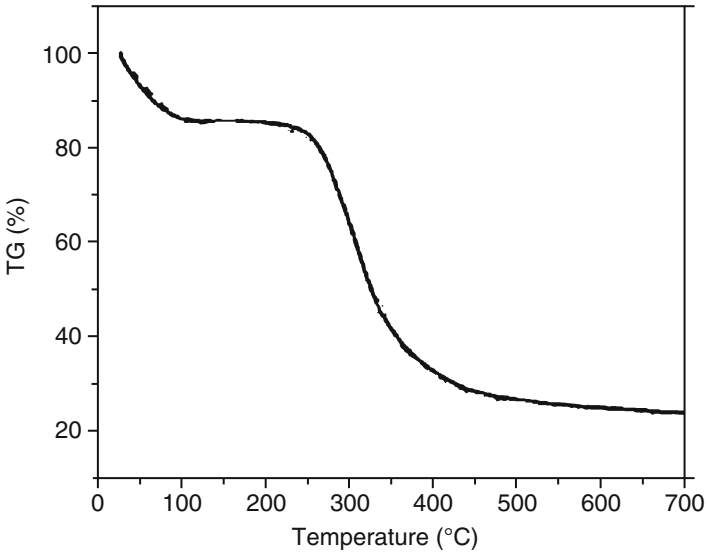

Fig. 6 TGA curve of bacterial cellulose

Table 4 Characterization of bacterial cellulose and its composites using TGA

Hydrogel	Condition	Results	Researcher
Bacterial cellulose collagen	Temperature range: 30–750 °C Heating rate: 10 °C min^{-1} Carrier gas: Helium	High thermal stability composite resulted by modifying BC with collagen	Albu et al. [60]
Bacterial cellulose phosphate	Temperature range: 40–500 °C Heating rate: 10 °C min^{-1} Carrier gas: Nitrogen	Composites containing up to 20% polyphosphate presents thermal stability similar to pure cellulose	Barud et al. [61]
Bacterial cellulose –polyvinyl alcohol	Temperature range: 25–400 °C Heating rate: 10 °C min^{-1} Carrier gas: Nitrogen	Introducing PVA in the BC/PVA system decreased the melting temperature (T_m) of the nanocomposite was decreased	Abidin et al. [62].
Methylated bacterial cellulose	Temperature range: 25–600 °C Heating rate: 10 °C min^{-1} Carrier gas: Nitrogen	Thermal stability of methylcellulose is equal to or higher than that observed for BC	Olievera et al. [63].
Bacterial cellulose gelatine	Temperature range: 25–700 °C Heating rate: 5 °C min^{-1} Carrier gas: Nitrogen	Gelatine and bacterial cellulose hydrogel Composites should be used at temperatures lower than 200 °C	Treesuppharat [10]

The amount of mass loss and the temperature differs following the method of bacterial cellulose fermentation, medium used, and also with addition of other materials to form composites. Table 4 listed previous researches on bacterial cellulose characterization using TGA.

3.3 Differential Scanning Calorimetry (DSC)

3.3.1 Introduction to Differential Canning Calorimetry (DSC)

Differential Scanning Calorimetry (DSC) measures the temperatures and heat flow associated with transitions in materials as a function of time and temperature.

It is a thermo-analytical technique which measured the difference in the amount of heat required to increase the temperature. The technique provides qualitative and quantitative information about physical and chemical changes that involve endothermic or exothermic processes or changes in heat capacity using minimal amounts of sample. It has many advantages including fast analysis time, typically 30 min, easy sample preparation, applicability to both liquids and solids, a wide range of temperature applicability, and excellent quantitative capability.

DSC enables the measurements of the transition such as the glass transition, melting, and crystallization. It allows accurate determination of temperatures associated with thermal events. Temperature can be calibrated with respect to one or more standards which allow highly accurate, precise, and reproducible values. DSC finds application in the pharmaceutical and health care industry as a means to determine purity of highly pure chemicals. Presence of an impurity leads to a decrease in melting point which can be related to percent purity. Water in oil emulsions can be evaluated by following the depression in freezing point of water. DSC is used to evaluate metal alloys and provide data required to prepare phase diagrams. Figure 7 shows schematic diagram of DSC.

DSC comprises the sample and reference holder, the heat resistor, the heat sink, and the heater. Heat of heater is supplied into the sample and the reference through heat sink and heat resistor. Heat flow is proportional to the heat difference of heat sink and holders. Heat sink has enough heat capacity compared to the sample. In case the sample shows endothermic or exothermic phenomena such as transition and reaction, this is compensated by heat sink. Thus the temperature difference between the sample and the reference is kept constant. The difference is the amount of heat supplied to the sample and the reference is proportional to the temperature difference of both holders. By calibrating the standard material, the unknown sample quantitative measurement is achievable.

The basic principle underlying this technique is that when the sample undergoes a physical transformation such as phase transitions, more or less heat will need to flow to it than the reference to maintain both at the same temperature. Whether less

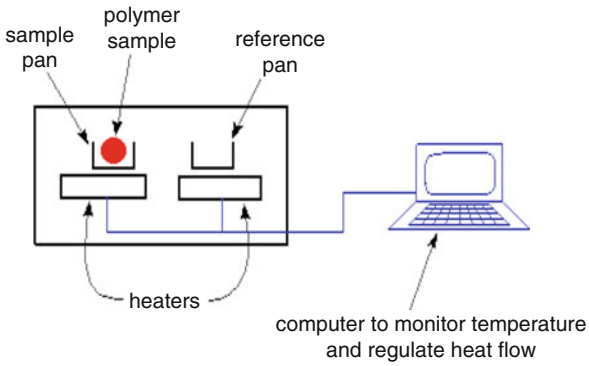

Fig. 7 Schematic diagram of DSC

or more heat should flow to the sample depends on whether the process is exothermic or endothermic. For example, as a solid sample melts to a liquid, it will require more heat flowing to the sample to increase its temperature at the same rate as the reference. This is due to the absorption of heat by the sample as it undergoes the endothermic phase transition from solid to liquid. Likewise, as the sample undergoes exothermic processes (such as crystallization), less heat is required to raise the sample temperature. By observing the difference in heat flow between the sample and reference, differential scanning calorimeters are able to measure the amount of heat absorbed or released during such transitions. DSC may also be used to observe more subtle physical changes, such as glass transitions. It is widely used in industrial settings as a quality control instrument due to its applicability in evaluating sample purity and for studying polymer curing.

3.3.2 Characterization of Bacterial Cellulose Hydrogel Using DSC

DSC was used in bacterial cellulose to define the glass transition temperature (T_g), melting temperature (T_m), and its crystallinity. Figure 8 shows the example of DSC curve. Glass transitions may occur as the temperature of an amorphous solid is increased. These transitions appear as a step in the baseline of the recorded DSC signal. This is due to the sample undergoing a change in heat capacity. As the temperature increases, an amorphous solid will become less viscous. At some point, the molecules may obtain enough freedom of motion to spontaneously arrange themselves into a crystalline form. This is known as the crystallization temperature (T_c). This transition from amorphous solid to crystalline solid is an exothermic process and results in a peak in the DSC signal. As the temperature increases, the sample eventually reaches its melting temperature (T_m). The melting process results in an endothermic peak in the DSC curve.

The states of water in a bacterial cellulose hydrogel give valuable information on the absorption, diffusion, and permeation properties of the hydrogel. The mechanical and physical properties of bacterial cellulose can change significantly upon water absorption due to the modification of the polymer chain structure. DSC is commonly

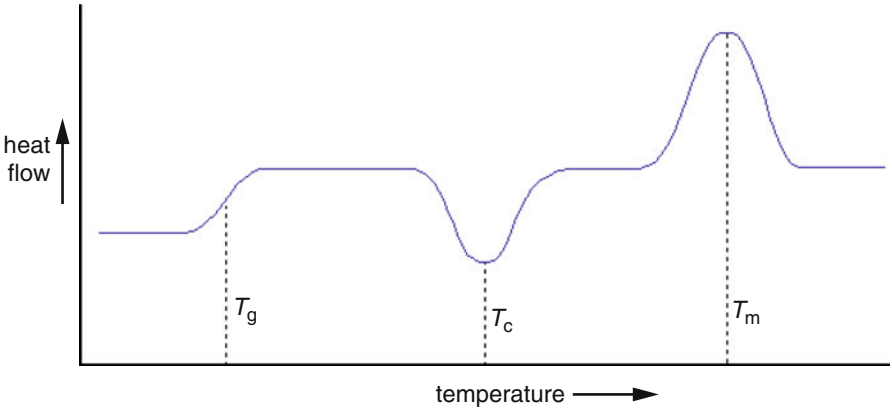

Fig. 8 Example of DSC curve

used tool to conduct such studies. During the interaction between water and polymer molecules, three forms of water are classified which are non-freezable water, freezable bound water, and free water. Non-freezable bound water is closely associated with a polymer matrix and does not show a phase transition by calorimetric analysis. Freezable bound water is the fraction bound to the matrix less closely and shows a melting and crystallization temperature remarkably different from bulk water. Free water shows similar melting/crystallization temperatures as bulk water. All considered, melting, crystallization, and glass transition (Tg) temperatures of water in hydrogels can reflect the state of the water-polymer interaction. Table 5 summarized previous work reported on the use of DSC to study the properties of bacterial cellulose and its composites.

Table 5 Characterization of bacterial cellulose and its composites using DSC

Hydrogel	Condition	Results 9			Researcher
		T_g °C	T_c °C	T_m°C	
Bacterial cellulose hydrogel	Temperature range: −50–600 °C Heating rate: 10 °C min^{-1} Carrier gas: Nitrogen	44.28	343.06	84.44	Mohite and Patil [64]
Bacterial cellulose-fiber composite	Temperature range: 20–400 °C Heating rate: 10 °C min^{-1} Carrier gas: Nitrogen	N/A	N/A	120–127	Nainggolan et al. [65]
Acelated bacterial cellulose	Temperature range: 25–500 °C	174–184	281–299	394–400	Barud et al., [66]
Hydrolyzed bacterial cellulose	Temperature range: −70–280 °C Heating rate: 20 °C min^{-1}	38.0	N/A	103.21	Auta et al. [67]
Bacterial cellulose –polyvinyl alcohol	Temperature range: 25–400 °C Heating rate: 10 °C min^{-1} Carrier gas: Nitrogen	N/A	N/A	275–250.3	Abidin et al. [62].
Bacterial cellulose-gelatin	Temperature range: 25–700 °C Heating rate: 5 °C min^{-1}	0.60	N/A	N/A	Treesuppharat et al. [10]

3.4 Thermomechanical Analysis (TMA) and Dynamic Mechanical Analysis (DMA)

3.4.1 Introduction to Thermomechanical Analysis (TMA)

Most materials undergo changes of their thermomechanical properties during heating or cooling. For example, phase changes, sintering steps, or softening can occur in addition to thermal expansion. TMA is another useful thermal analysis technique used in materials characterisation. It is used to characterize linear expansion, glass transitions, and softening points of materials by applying a constant force to a specimen while varying temperature. The sensitive nature of this technique in either the penetration or expansion modes offer certain advantages which allow measurement of dimensional changes even in thin films and coatings.

TMA analyses can hereby provide valuable insight into the composition, structure, production conditions, or application possibilities for various materials including hydrogel. The application range of instruments for thermomechanical analysis extends from quality control to research and development. Hydrogel properties that can be measured by TMA include thermal expansion, the thermal shrinkage, the glass transition, curing reaction.

Figure 9 shows the schematic diagram of TMA. The sample is inserted into the furnace and is touched by the probe which is connected with the Length Detector and the Force Generator. The thermocouple for temperature measurement is located near the sample. The sample temperature is changed in the furnace by applying the force

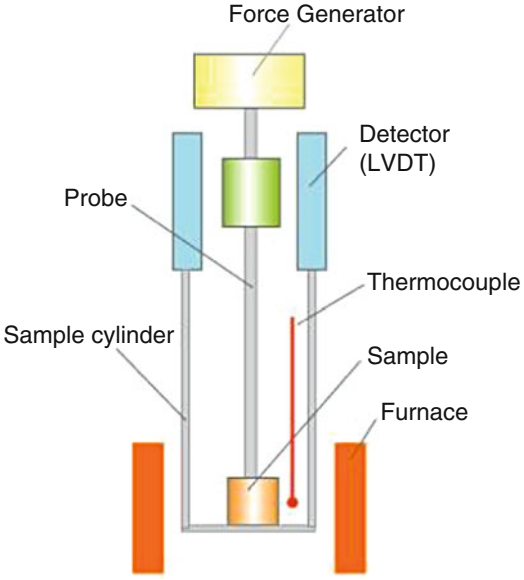

Fig. 9 Schematic diagram of TMA

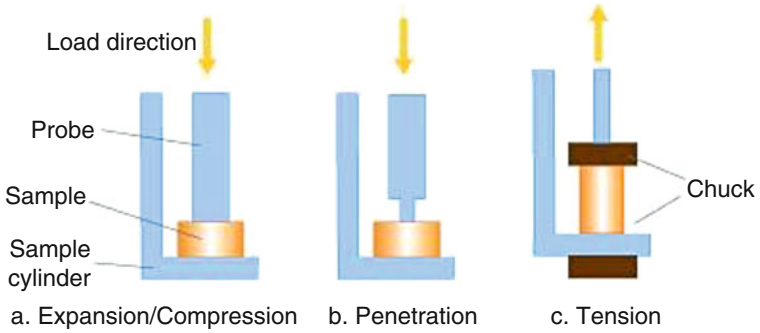

Fig. 10 TMA probe types

onto the sample from the Force Generator via probe. The sample deformation such as Thermal Expansion and Softening with changing temperature is measured as the probe displacement by the Length Detector. Linear Variable Differential Transformer (LVDT) is used for Length Detection sensor.

There are several types of the probe for TMA as shown in Fig. 10. The materials of probes are usually from quartz glass, alumina, and metals. The choice of the probes is dependent on the measurement purpose as stated blow:

(a) Expansion/Compression Probe:
It is used for the measurement of the deformation by the thermal expansion and the transition of the sample under the compressed force is applied.
(b) Penetration Probe:
It is used for the measurement of the softening temperature.
(c) Tension Probe:
It is used for the measurement of the thermal expansion and the thermal shrinkage of the sample such as the film and the fiber.

3.4.2 Introduction to Dynamic Mechanical Analysis (DMA)

The properties of hydrogel materials or composites need to be study in order to predict their performance over the lifetime of the specific application. Often short-term test information is used to project long-term high-temperature performance. These may have severe limitations. Dynamic mechanical analysis (DMA) can continuously monitor material modulus at different applied frequencies and hence provides a more realistic indication of properties. DMA is a technique that measures the modulus (stiffness) and damping (energy dissipation) of materials as they are deformed under periodic stress. Some hydrogels which are viscoelastic in nature are subject to time, frequency, and temperature effects on mechanical properties which can be analyzed by this method. Some of the properties which can be measured by

the technique are glass transition, softening, viscosity and degree of cure, and stress relaxation.

DMA can be used to analyze a wide variety of materials in different forms. It finds application in Research and Development for the investigation of material structure, their development, selection for specific end-uses, comparative evaluations, and material lifetime predictions. It is also used in quality control for process simulation and optimization, incoming, and in process material certification and troubleshooting. DMA allows a quick comparison of material properties between two dissimilar or two similar materials processed differently. Since samples can be tested in the form of bars, films, fibers, and viscous liquid samples, the technique comes closest to the actual application envisaged and results therefore reflect the actual application. Figure 11 shows DMA instrumentation and its schematic diagram.

The sample is clamped in the measurement head of the DMA instrument. During measurement, sinusoidal force is applied to the sample via the probe. Deformation caused by the sinusoidal force is detected and the relation between the deformation and the applied force is measured. Properties such as elasticity and viscosity are calculated from the applied stress and strain plotted as a function of temperature or time.

DMA is used for measurement of various types of materials using different deformation modes. There are tension, compression, dual cantilever bending, 3-point bending, and shear modes as shown in Fig. 12.

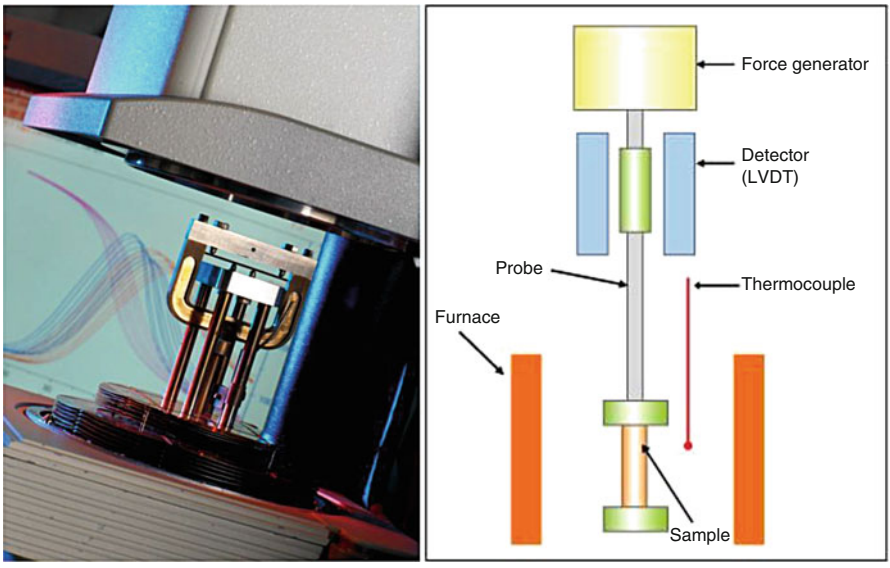

Fig. 11 Dynamic mechanical analysis and schematic diagram of DMA (Tension mode)

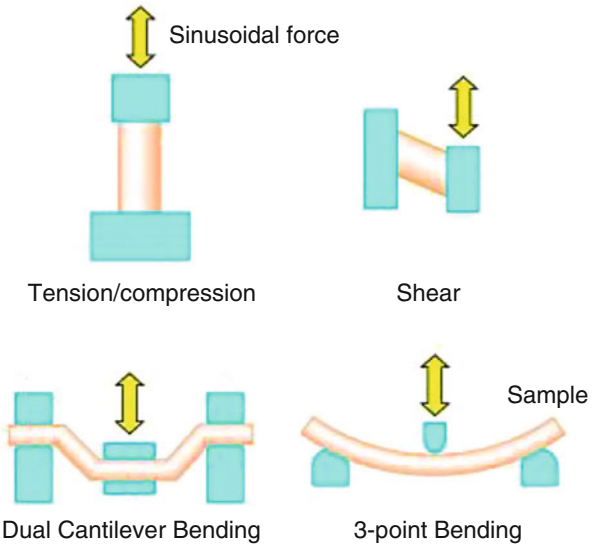

Fig. 12 DMA deformation modes

3.4.3 Characterization of Bacterial Cellulose Hydrogel Using TMA and DMA

DMA and TMA were capable to provide important mechanical properties such as tensile strength and strain test of hydrogel. For example, Numata et al. [68] used TMA to determine the change from the solid state to gel state of bacterial cellulose-polyethylene glycol diacrylate (PEGDA) composites. The TMA results indicate that the elasticity of the sample in the gel state was decreased by cross-linked PEGDA. Other researchers measured coefficient of thermal expansion (CTE) of bacterial cellulose sheets using TMA [69]. This result suggested bacterial cellulose nanocomposite as a promising candidate for flexible organic light emitting diode substrate.

The use of DMA had been employed by Mulijadi et al. [70] to studies mechanical properties of bacterial cellulose composites. The composites were synthesized through cross-linking of aqueous solution of acrylamide using gamma ray. Authors reported that increased dose of irradiation will increase tensile strength of the bacterial cellulose composites and it decreased at maximum point. DMA also had been used to determine the viscoelastic behavior of the bacterial cellulose-polylactide green nanocomposites [71]. The use of BC to reinforce PLLA matrix resulted in a much stiffer material compared to the neat PLLA. Authors also reported failure of DMA analysis on lower percentage of polylactide addition due to the brittleness of the samples.

4 Conclusion

The studies on thermal performance of hydrogel allowed fabrication of various composite hydrogels. With the development of new technology, this strategy is suitable for fabricating novel cellulose-based hydrogels with multifunctional

properties. Cellulose-based hydrogels have many favorable properties such as hydrophilicity, biodegradability, biocompatibility, transparency, low cost, and nontoxicity. Furthermore, bacterial cellulose hydrogel can be used as matrices to incorporate inorganic nanoparticles for preparing cellulose-inorganic hybrid hydrogels. Bacterial cellulose acts as a thermal stabilizer for overall composite hydrogel matrix. It interacts synergistically leading to composites with improved thermal properties. On the other hand, the bacterial cellulose sheet impregnated with other gel formed matrix has a significantly improved thermal stability. This allowed fabrication of hydrogel which exhibit smart properties on temperature sensitivity or ideally dual (pH/temperature) sensitivity. The end product can be potentially applied as an on–off switch triggered by the environment stimuli such as heat or temperature to deliver drug or active species, for example, antibacterial agent, antioxidant, or antiperspirants.

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Structure Response for Cellulose-Based Hydrogels via Characterization Techniques

25

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Abstract

Hydrogels are three-dimensional cross-linked polymeric networks capable of imbibing substantial amounts of water or biological fluids and are widely used in biomedical applications, especially in pharmaceutical industry as drug delivery systems. Although their solvent content can be over 99%, hydrogels still retain the appearance and properties of solid materials, and the structural response can include a smart response to environmental stimuli (pH, temp, ionic strength, electric field, presence of enzyme, etc.) These responses can include shrinkage or swelling. Cellulose-based hydrogels are one of the most commonly used materials and extensively investigated due to the widespread availability of cellulose in nature. Cellulose is the most abundant renewable resource on earth that is intrinsically degradable. Additionally, the presence of hydroxyl groups results in fascinating structures and properties. Also, cellulose-based hydrogels with specific properties can be obtained by combining it with synthetic or natural polymers. This chapter surveys different characterization for cellulose hydrogels and the structure-response relationship. As such we would describe the techniques involved for characterizing cellulose-based hydrogels and their response in terms of their morphology such as polarized optical microscopy (POM), scanning electron microscopy (SEM), and transmission electron microscopy (TEM), their stability by thermal properties (often with differential scanning calorimetry, DSC), and structure response such as Fourier transform infrared spectroscopy (FTIR) and nuclear magnetic resonance (NMR). In addition, we give a focus on measuring the mechanical properties of superabsorbent hydrogels giving examples with cellulose where applicable. Finally, we describe the techniques for analyzing biological techniques and the applications with cellulose.

Keywords

Characterization · Cellulose analysis · Structure-response · Hydrogels · Materials

1 Introduction

A representative of the kingdoms Plantae, Animalia, and the Eubacteria domain synthesizes cellulose and is the most abundant product on earth. Although these different sources of cellulose have many varieties, they share many characteristics. Cellulose can be characterized biochemically as polysaccharide with a

β-1,4-glycosidic linkage, which is formed by condensation and polymerization of long anhydroglucose chain units [1].

Cellulose is associated with biopolymer due to the many characteristics of benefit to the formation of a hydrogel. Such characteristics include availability in abundance, renewability, biocompatibility, biodegradability, nontoxicity, and many more unique features, which are not easily acquired through chemical synthesis [2].

Hydrogels can be defined as three-dimensional cross-linking networks of polymers that can absorb and retain water. Hydrogels have potential applications in several areas, including medical, pharmacology, and agriculture areas. Due to hydrogel water retention properties and diffusion system, it can be used as drug delivery systems, microfluidic devices, biosensors, tissue implants, and contact lenses [3].

Hydrogels can modify their water retention and release capacity in response to external stimuli such as temperature, pH, and ion concentration. To reduce the toxicity or bioinert impact of these external factors, hydrogels are often co-polymerized with various biopolymers, including cellulose which has been widely used and studied [4].

This chapter aims to investigate the mechanisms involved in the characterization of cellulose-based hydrogels, describing the effect in terms of their structure response.

2 Cellulose-Based Hydrogels

There are many variations of cellulose that can be used in the preparation of hydrogels, including native cellulose, bacterial cellulose, and cellulose derivatives. The main difference between these variations is in terms of the solubility; the native cellulose presents a major challenge as it is not easily dissolved at common solvents due to its highly extended hydrogen bond structure [5].

The cellulose produced by bacteria, such as the genus *Acetobacter xylinum* or bacterial cellulose, is a natural polymer which consists of a three-dimensional network of polymers that are able to retain up to 99% of its weight in water. Bacteria cellulose have high strength mechanical properties and excellent biocompatibility; these polymers can be used as tissue repair and implants [6].

The production of cellulose-based hydrogels occurs through physical cross-linking; this is possible to achieve due to the large number of hydroxyl groups in cellulose, which can form hydrogen bonds that easily link its chains [5].

The morphology of cellulose-based varieties of hydrogels is complex. Commonly to the geometry includes fibers, films, membranes, sponges, and beads [7]. The bacterial cellulose due to its high properties such as mechanical, swelling, crystallinity, and biocompatibility has an extended application spectrum and can be used in tissue engineering [8] and implants [9].

The addition of cellulose and its derivatives can tailor its structure for the application intended, among them includes its swelling capacity and drug delivery. These favor its use mainly in the areas of agriculture [10] and horticulture [11]. Among other functions, cellulose-based hydrogels have also been widely used as for drug or protein delivery systems, including different routes of application

such as transdermal and oral [1]. In addition, many other applications are currently used cellulose-based hydrogels such as photonic materials responsive to stimuli, which can be tailored to have their functions altered by an external stimuli [12].

3 Morphology Analysis

Visual information of hydrogels at the nanoscale is extremely important to understand the morphology such as pore size distribution, fiber dimensions, distribution of fillers, and/or nanoparticle second phases. In addition, it can also provide important information in terms of drug encapsulated into the hydrogel structure while also can clarify results of different characterization techniques, such as nanoindentation or biology tests.

3.1 Polarized Optical Microscopy (POM)

Light-sensitive hydrogels have applications in sensors, optical filters, inks, displays, and other technologies. Biopolymers can be incorporated into the hydrogels to improve their mechanical properties, as well as stimulate the formation of chiral nematic liquid crystals, which have unique and valuable photon properties, including manipulating the hydrogel response to external stimuli [13].

Tatsumi et al. (2012) used polarized optical microscopy (POM) to observe and characterize the phase of chiral nematic formation during the production of composites comprising poly(2-hydroxyethyl methacrylate) (PHEMA) and cellulose nanocrystallites (CNC), with the objective to evaluate the ability of this biopolymer to control the hydrogel response to external stimuli [14]. In addition, POM also allows to observe any tension or residual stress into the hydrogel structure as observed in Fig. 1. These residual stresses are important parameters to identify points of fracture and the limit of failure of the polymeric materials.

Kelly et al. (2013) detected through POM that after the addition of nanocrystalline cellulose in the monomer of acrylamide and cross-link, it promotes a strong red birefringence due to the intrinsic birefringence of the cellulose nanocrystals to this color. This is an important characteristic since the polarization time is correlated to the swelling, which allows controlling this capacity according to the light stimulus [12].

3.2 Scanning Electron Microscopy (SEM)

Scanning electron microscope (SEM) is a widely used technique when analyzing different formulations of hydrogels since it can provide important data on structural characteristics of these products. In addition, SEM can identify key differences in surface morphology, size, shape, and porosity of hydrogels according to the association of polymers used [10].

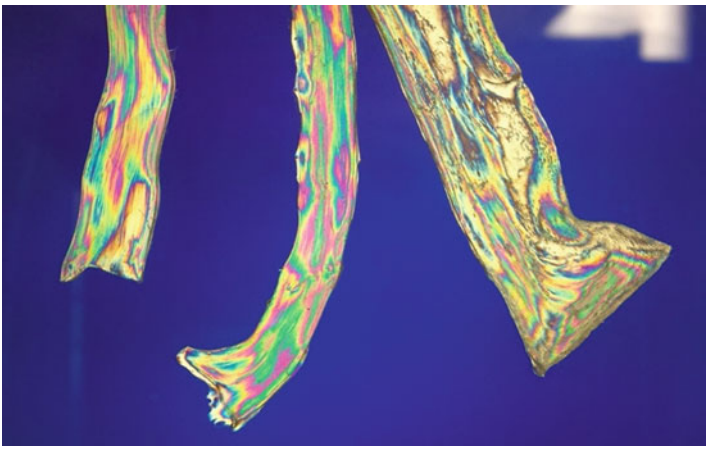

Fig. 1 Polarized optical microscope from superabsorbent hydrogel composing of PVA + Cellulose. (Original artwork)

Demitri et al. (2016) observed through the SEM that adding sodium salt of carboxymethylcellulose (CMCNa) in polyethylene glycol diacrylate (PEGDA700) hydrogels promotes a significant increase in density of the material. Furthermore, the network structure increased the number of pores and consequently the contact area of the hydrogel, favoring the absorption of water [15].

Figure 2 exhibits a hydrogel with cellulose and it illustrates the porous characteristic of cellulose-based hydrogels. This property, provided by the addition of this biopolymer, brings great advantages for many applications in several areas, especially those in which a greater capacity to retain water is required [16].

3.3 Transmission Electron Microscopy (TEM)

Unlike SEM, which basically characterizes the morphology of the sample surface, TEM collects information about a deeper internal composition of the samples which improves the understanding of these structures in terms of their morphology, crystallization, and magnetic domains. Images obtained with TEM have a very high definition [1].

The use of TEM can characterize and contribute to the understanding of the behavior of compounds such as cellulose nanocrystals, which are promising alternatives in the manufacture of various products. Through this technique, it is possible to observe its role of induction in the formation of chiral materials during the hydrogenation of prochiral ketones [17]. Li et al. (2017) investigated through TEM on cellulose nanocrystals with carbon-dot hydrogels a tendency of fiber formation with large dimensions, being able to reach values of the diameter of 5–10 nm and length of 140–260 nm [18]. However, cellulose is also added to the hydrogel structure due to its high water solubility, low cost, and high swelling

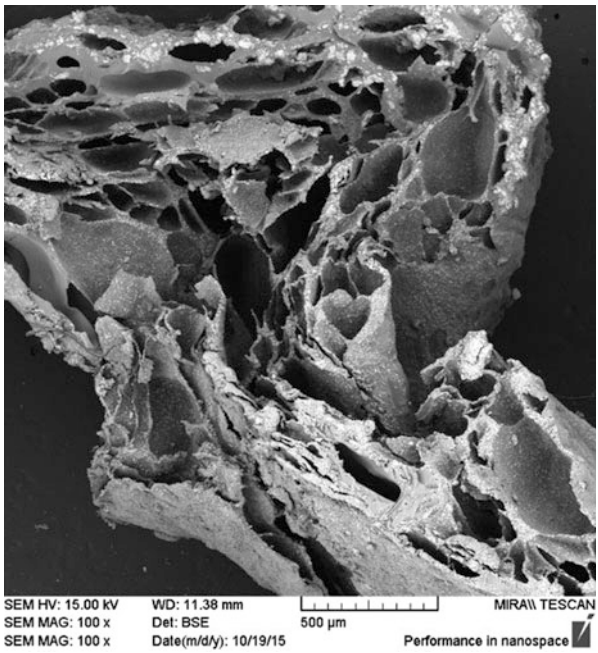

Fig. 2 Internal structure of a superabsorbent hydrogel after dehydration. (Original artwork)

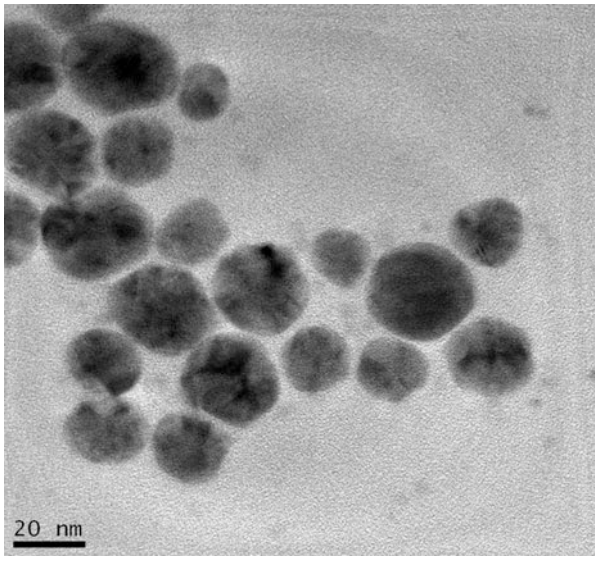

Fig. 3 TEM image of polyvinyl pyrrolidone (PVP) cross-linked with carboxymethyl cellulose (CMC) and silver nanoparticles (AgNP). (Original artwork)

capacity [19]. This further improvement in swelling can help in wound healing to keep a wound moisture environment while also able to target deliver a drug, such as exhibited in Fig. 3 where it is possible to observe silver nanoparticles in between the structure of cellulose hydrogel.

4 Swelling Characterization

When a hydrogel is in contact with solvent molecules, the solvent initially penetrates the hydrogel surface. In this case, the unsolvated glassy phase is separated from the rubbery hydrogel region with a boundary move. In other words, swellability is based on ease of migration of water from surrounding areas into the preexisting hydrogel chain spaces. The process involves segmental motion of water that results in greater separation distance between these chains. Against the favorable osmotic force, there is an opposite elasticity force, which balances the stretching of the network and prevents its deformation. At the equilibrium where the elasticity and osmotic forces are balanced, there is no additional swelling [20]. Swelling profile of hydrogels can significantly affect the mechanical properties and subsequent cell attachment, migration, and neovascularization [21] and, therefore, must be considered when synthesizing the hydrogel scaffold.

One of the most important characterizations of superabsorbent hydrogels is to understand the swelling kinetics since, on these polymers. In effect, preserving the shape is maintained after water absorption and swelling. The swollen gel strength should be high enough to prevent a loosening, mushy, or slimy state.

Tests of swelling are one of the easiest techniques to analyze from a hydrogel, and the measure occurs by pre-weighting samples which are then immersed into a solution, which can be buffer solutions or distilled water, and after removing the excess surface water of the hydrogel, they are measured at various time intervals over a 24-h period. With these values, it is possible to obtain the swelling percentage; although, with superabsorbent hydrogels, some parameters are added to analyze if these hydrogels hold the values under pressure. A cylindrical solid load is put on dry superabsorbent hydrogels while it can be freely slipped in a glass cylinder. Saline solution (0.9% NaCl) is then added when the liquid level is equal the height of the sintered glass filter. After 60 min, the swollen particles are weighed again, and absorbency under load is calculated based on the final and initial weights.

The work performed by Cipriano, B. H. et al. (2014) exhibited a superabsorbent hydrogel (Fig. 4) with a gel based on N,N-dimethylacrylamide (DMAA) with sodium acrylate (SA) and potassium persulfate (KPS) that can swell up to ten times its size when immersed in water and is robust enough that it can be held in one's hands [22].

5 Structure Analysis

To understand many features that hydrogel possess, it is necessary to analyze its structure, and for that, many characterization techniques are available with key differences and advantages, depending as to what is to be understood from the hydrogel. The most important characterization techniques for cellulose hydrogels are described in Table 1.

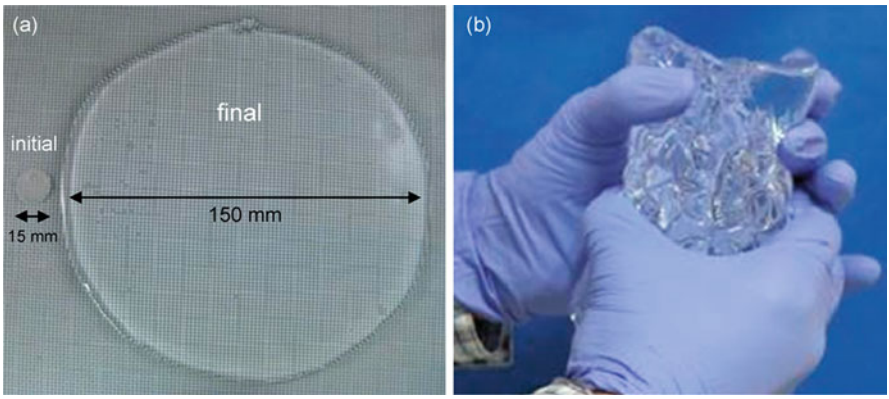

Fig. 4 (**a**) DMMA-SA + KPS hydrogels before and after the swelling tests; after swelling equilibrium (**b**) the hydrogel can withstand the pressure of the hands and is malleable. (Reprinted with permission from [22]. Copyright © 2017, ACS)

Table 1 Structure characterization techniques for cellulose hydrogels

Equipment	Basic principle	Key analysis
Nuclear magnetic resonance (NMR)	Measurement of absorption of radiofrequency radiation by a nucleus in a strong magnetic field. Spectroscopy of nuclear spin states	Obtain molecular organization, interactions, and mobility of gel constituents
Fourier transform infrared spectroscopy (FTIR)	Measurement of absorption of infrared spectrum via emission of a solid, liquid, or gas	Obtain chemical structure of the hydrogels, such as chemical bonds
Ultraviolet-visible spectroscopy (UV-vis)	Measurement spectroscopy in the ultraviolet-visible spectral region	Quantitative determination of different analytes and biological macromolecules
Circular dichroism (CD)	Absorption difference between the left and right circularly polarized light which occurs if a molecule possesses one or more chiral chromophore	Obtain information about chiral molecules and useful for analyzing secondary structures of macromolecules
Fluorescence spectroscopy (FS)	Measures the molecular absorption of a light energy at one predetermined wavelength	Quantitative determination of different analytes with accurate results

5.1 Nuclear Magnetic Resonance (NMR)

The nuclear magnetic resonance (NMR) technique analyzes magnetic fields through specific resonance frequencies that are emitted and reabsorbed depending on sample

field strength and magnetic properties, which can characterize complex systems of polymers or isolated biopolymers of plants [2].

The NMR spectra supplement important information for the characterization of hydrogels; it is through the changes observed in the lines of this spectrum that one can suggest if changes occurred in the chemical structure of these polymers, often using external stimuli hydrogels, to investigate the continuity on the chemical integrity or if some chemical reaction occurs between the polymeric chains [18].

For cellulose-based hydrogels, NMR indicates, in addition to other properties, good chemical stability since no reactions are observed between the most common hydrogels even when exposed to temperature ranges of 150 to 190 °C. This is concluded by the results at the end of the analysis, where samples have the same chemical structure when compared with the beginning [23].

Through NMR it is possible to analyze the interference of the association of other polymers, such as cellulose, on the molecular mobility of hydrogels. The addition of cellulose nanowhiskers into gelatin promotes an increase in the stiffness, to the same extent that it decreases its mobility [24].

NMR can also be used to verify the integrity and structural behavior of hydrogels during some external stimuli. The addition of cellulose nanocrystals in the carbon-dot hydrogel formulation promoted a considerable thermal resistance to the product; typical cellulose bands are observed in samples subjected to hydrothermal carbonization (up to 240 °C) [18].

5.2 Fourier Transform Infrared Spectroscopy (FTIR)

Fourier transform infrared spectroscopy (FTIR) is a technique which has been commonly used for characterization of hydrogels. This technique provides the absorption peaks corresponding to frequencies of vibrations between the bonds of atoms. Furthermore, a unique spectrum is created for each material, therefore enabling accurate identification of the materials and characterization.

The use of FTIR for characterization of hydrogels consists of investigating and evaluating the chemical structural surface of the functional polymer groups. This effective technique obtains the spectra of absorption, emission, and photoconductivity of materials in any physical state, giving relevant information on the molecular structure of polymers [16].

Studies performed via incorporation of cellulose nanocrystals on carbon-dot hydrogels exhibited thermal resistance, which provided similar bands in FTIR spectra between the hydrogels before and after the hydrothermal treatment (180–240 °C). In addition, the hydrogel maintained the main functional groups of the cellulose, without altering the main structure. However, an alteration was noticed when the hydrothermal treatment was raised to 260 °C, which carried the hydrogel to a complete hydrothermal carbonization [18].

It is also possible with the FTIR analysis to evaluate the interaction between different compounds and polymers in between the hydrogels. For example, the association of cellulose hydrogel with hydroxyapatite for application in biomedical area is possible to identify through peaks in FTIR spectra, and it can confirm the interaction between these two materials, suggesting an association capacity of cellulose [25].

5.3 Ultraviolet-Visible Spectroscopy (UV-Vis)

The evaluation of hydrogels on ultraviolet light is an interesting alternative to evaluate drug delivery mechanisms. UV-Vis occurs by passing a light through a specific region of the degraded or diluted polymer solution or drug. The light absorbed by a molecule of the compound can go from its ground state to an electronically excited state, and this information is stored by a detector which quantifies these parameters. For the majority of conjugated molecules, its photon absorption energy falls within the range of near UV and visible light [26].

Characteristics of cellulose-micelles or dendrimers can be evaluated using UV-Vis, sharing important information such as density values and hydrogel efficiency of drug loading [26]. In addition, it can also hold important information in terms of concentration of nanoparticles incorporated into the hydrogel material.

Raghavendra et al. (2013) utilized gum acacia (GA) and gaur gum (GG) in various concentrations to incorporate and form silver nanoparticles from silver nitrate ($AgNO_3$). Confirmation of silver nanoparticle formation was obtained via UV-Vis, and the process of formation Ag + ions to silver nanoparticles is due to the reduction action of functional groups present in GA and GG, where the pendent hydroxyl groups were involved in the reduction factor. Increasing the molecular weight had to obtain more stable silver nanoparticles [88].

It is understood that there is a relationship between the wavelength emission of a polymer or hydrogel and its structural characteristics that emission can still be influenced by the environment or not. The nanocellulose-based hydrogels can stabilize other compounds when associated, preventing their aggregation; this capacity is related to the carboxylic groups of the cellulose, the result of which is a higher molecular organization, consequently causing a larger wavelength emission [27].

5.4 Circular Dichroism (CD)

Circular dichroism is a spectroscopy technique which characterizes the structure of polymers using the variation of polarized light absorption. Cellulose-based hydrogels tend to demonstrate a strong positive ellipticity, arising from the direction of reflection from left-handed circularly polarized light in chiral nematic phase [12].

The circular dichroism on hydrogels evidences the organization or molecular disorganization on the structure. These evaluations can still be performed on different conditions, where the molecular organization's response to external stimuli is

observed, and it is possible to perceive a variation of the molecular order according to the temperature [12]. Hydrogels based on cellulose tend to present a high molecular organization.

5.5 Fluorescence Spectroscopy (FS)

Fluorescence spectroscopy (FS) is a technique that consists of exposing the sample to a beam of light, most often ultraviolet light or visible light, causing an excitation of the molecules of the polymers, and once stimulated, reaction occurs, and FS is done by measuring the light emitted from a sample after absorbing light at a higher energy than it is emitting [18].

Hydrogels based on nanocrystal cellulose and acrylamide demonstrate excellent photoluminescence properties by showing a direct relationship between emission wavelength and maximum intensity with excitation wavelength. This characteristic of cellulose nanocrystal-based hydrogels can be related to the surface with energy traps through incomplete reactions and due to the radiative recombination of electrons and holes [27]. It is possible that polycyclic aromatic compounds also have an influence on the behavior of these hydrogels [28].

It can be noticed that the emission properties of the hydrogels based on cellulose nanocrystals are influenced by external stimuli, among them the pH; this is due to changes in the surface properties of these products as well as in the electronic transitions of these products [18]. The increase in pH causes a decrease in emission intensity but does not influence on the wavelength [28].

6 Cellulose Hydrogels and Mechanical Properties

6.1 Key Aspects of Measuring Mechanical Properties on Superabsorbent Hydrogels

Superabsorbent gels can have a swelling ratio in the order of 100–1000 for many gels, which is inversely proportional to the cross-linking density [22]. As the cross-linking density increases, the gels become soft and floppy and can be a challenge to work with as they tend to be slippery and difficult to grasp. However, gels that are highly cross-linked tend to be stiff, but they are also generally quite brittle and tend to decrease its sensor capabilities [29]. This brittleness occurs due to the free-radical polymerization, and the cross-linking in these structures is heterogeneous with many chain loops. If this gel is deformed, chain segments could deform more than others, leading to zones with high stress leading to possible failure at low deformations [30].

Most polymers are relatively poor in terms of mechanical properties in order of KPa [31] compressive strength and if the polymer is designed for biomedical applications such as bone healing – the bone is in the order of 170 MPa innovations with the polymer are necessary [32].

Another important aspect of measuring mechanical properties of hydrogels is that due to the relatively low pore sizes (1–100 nm range), it is one of the easiest ways to obtain the values of the behavior of the hydrogel network (such as mesh size, volume swelling coefficient, molecular weight between two adjacent cross-linking points) [31].

Measurement of mechanical properties needs to be evaluated carefully since they are time-dependent due to the viscoelasticity of the polymer network and time-dependent deformation fluid flow [31]. To exemplify the importance of this topic, hydrogels for tissue engineering tend to lack mechanical properties [33]; however, as cells proliferate and elongate on the hydrogel implant, they improve the mechanical properties as the time passes via reorganization of fibers and production of extracellular matrix [34, 35].

Water evaporation can also affect the measurements of the hydrogel if these are performed in the swollen state [36]. Furthermore, further compression of the hydrogel could change the structure, and the process is irreversible as it will be discussed.

6.2 Universal Test-Frame

Universal test-frame is the most common tool for mechanical characterization of materials which can perform several techniques such as tensile, compression, adhesive strength, torsion, among others. For tensile tests (Fig. 5a), the technique consists in applying a tensile force to the extremities of the material which are held between two grips. However, hydrogel samples tend to be hydrated which makes it difficult to grip, so cardboards are used or performed with glue [31]. With this technique, a chart of stress-strain is obtained, and values of Young's modulus, yield strength, and maximum elongation at break are derived from the data tested. This test has some issues as it destroys the sample, and only once it is possible to study each specimen, in terms of studying the hydrogel mechanical properties over time this test is not advised.

Bacterial cellulose possesses higher water holding capacity and superior tensile strength compared to plant cellulose [37]. In addition, bacterial cellulose has mechanical properties such as tear resistance, which is superior to many synthetic materials [38]. For these reasons, researchers developed a tube-shaped cellulose and assessed its potential as a substitute for blood vessels [39, 40] which demonstrated values of tensile strength around mN which is comparable to those of normal blood vessels; it could withstand the blood pressure of a rat [41]. Results showed that after 4 weeks, the tube was covered with oriented endothelial cells which enhances the stability under shear stress that occurs when blood flows through these vessels.

More recently, researchers have been investigating cellulose nanocrystals which are produced from chemical treatments from pulp cellulose fibers. These nanocrystals possess many desirable properties, such as high tensile strength (7500 MPa) and high stiffness (Young's modulus up to 140 GPa) with an abundance of surface hydroxyl groups [42, 43]. The addition of these nanocrystals into synthetic hydrogels can improve mechanical properties and exhibit controllable swelling ratio [44, 45].

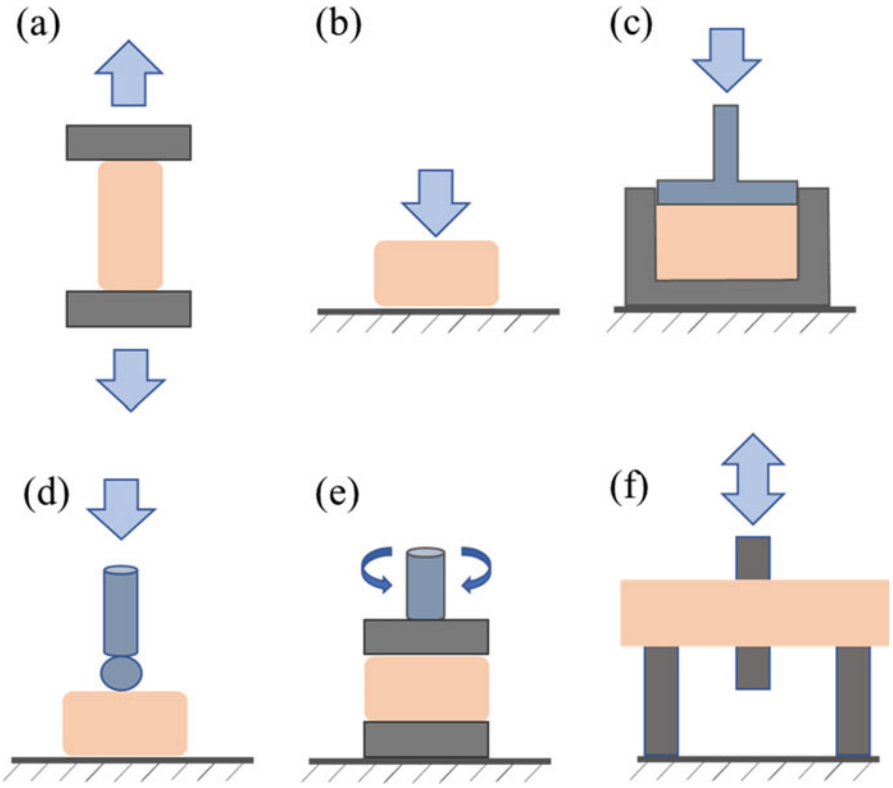

Fig. 5 Different types of tests that can be performed for mechanical properties. (**a**) Tensile; (**b**) compression; (**c**) confined compression; (**d**) indentation; (**e**) rheology; (**f**) dynamic mechanical analysis

In addition to tensile tests, universal test-frame can also measure compression tests (Fig. 5b). In compression tests, values are obtained by the pressure applied to the surface of the hydrogel and distance which is compressed. Compression tests, however, have several limitations when testing hydrogels, such as expanding under compression, and pressure might not be applied evenly. These limitations result in high standard deviation values if the sensor of the machine is not very precise. To overcome these problems, samples are normally measured in a dry state, or in a confined compression chamber (Fig. 5c), after it reaches the equilibrium swelling ratios to improve its precision [46].

Superabsorbent hydrogels have many applications in agriculture due to the need of reducing water consumption and optimize water resources. The ability to store large quantities of water from these hydrogels makes it excellent in this field; moreover, these hydrogels store water even under significant compression [37]. The compressibility of a structure is also an indicator of the rigidity of a foam, and cellulose hydrogels not only can improve the swelling capabilities of a synthetic polymer but also its stiffness [47].

6.3 Instrumented Indentation

Instrumented indentation is a versatile technique that aims to measure elastic and plastic properties in micrometric and nanoscales. It is an expansion of the capabilities of the traditional hardness test and consists of penetrating a diamond tip into the material, controlling and recording the load and the depth of penetration on nanometer scale with large amount of data (Fig. 5d), which are plotted in a force-displacement diagram, forming a load-unloading curve. It is used to measure mechanical properties of materials with modified surfaces, thin films, among others [48].

As this technique involves some knowledge of mathematical models, some brief introduction to the theoretical methods will be given.

Figure 6 exhibits the surface of a sample after being penetrated by an indenter to the depth h of the surface due to the application of a force P. At this depth, there is elastic and plastic deformation forming an impression of the formed tip used for any depth of contact h_c. After the tip is removed, the part of the material that has suffered elastic deformation is recovered.

In Fig. 6, h_c is the contact depth between the tip and the sample, h_s is the displacement of the contact perimeter surface. The depth h is related in Eq. 1

$$h = h_c + h_s \tag{1}$$

After removal of the tip and recovery of the elastic deformation, a final residual impression remains. As E_R corresponds to elastic recovery, the relationship between these magnitudes is related in Eq. 2:

$$h_{\max} = h_f + h_s = h_c + h_s \tag{2}$$

The deformation of the diamond tip, however small, should be taken into account, where it is necessary to define Eq. 3:

$$\frac{1}{E_R} = \frac{1-\nu^2}{E^*} + \frac{1-\nu_i^2}{E_i^*} \tag{3}$$

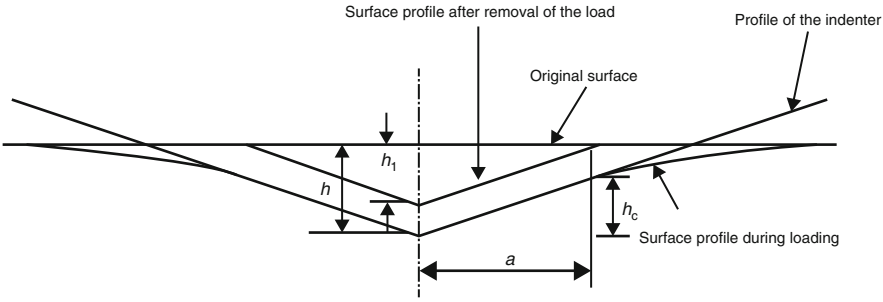

Fig. 6 Schematic of a section in two moments of a penetration. (Original artwork)

E is the modulus of elasticity, v the Poisson's ratio of the sample, and v_i, E_i, and E_r correspond to the Poisson's ratio, elastic modulus of the tip, and reduced modulus of the indenter set and sample, respectively.

The graph of Fig. 7 exhibits a loading-unloading cycle (load applied as a function of the stress). The contact stiffness S can be determined using the maximum loading point of the unloading curve, that is, it corresponds to the slope of the first moments of the elastic recovery as related to Eq. 4:

$$S = \frac{dP}{dh} \tag{4}$$

That is also related to the reduced module [49], by Eq. 5:

$$S = \beta \frac{2}{\sqrt{\pi}} E_r \sqrt{A} \tag{5}$$

where A is the contact area designed for maximum load and β is a dimensionless constant that corrects deviations in stiffness caused by the lack of axial symmetry of pyramidal indenters. This evaluation is made during the contact and not after the tip removal.

Assuming that the tip does not deform significantly, A is a function of the depth of contact between indenter and sample, which is obtained during tip calibration by Eq. 6:

$$A = F\left(h_c\right) \tag{6}$$

where hc is the depth of contact related to Eq. 7:

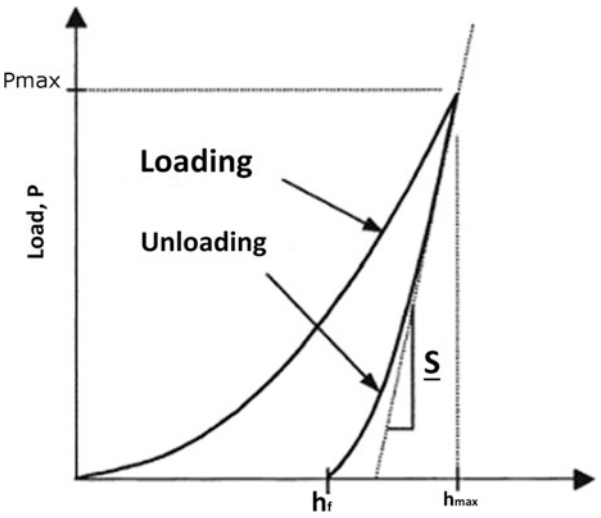

Fig. 7 Schematic representation of a load curve P by a displacement h for a complete load-discharge cycle [50]. (Original artwork)

$$h_c = h_{\max} - h_s \tag{7}$$

the deflection of the surface h_s in the perimeter of contact depends on the geometry of the penetrator and is related via Eq. 8:

$$h_s = \varepsilon \frac{P_{\max}}{S} \tag{8}$$

The ε is a constant with a value of 1.0 for flat tips, 0.75 for paraboloids of revolution, and 0.72 for conics; $P_{\max}$ is the maximum applied load.

By extracting the values of $P_{\max}$, $h_{\max}$, and S from a load-unloading curve, the elastic modulus E of the material is calculated from the combination of expressions (3) and (8). The hardness H is given by Eq. 9, load $P_{\max}$:

$$H = \frac{P_{\max}}{S} \tag{9}$$

Instrumented indentation for superabsorbent hydrogels has several advantages over other conventional mechanical characterization techniques [33, 51] such as quick, online, and real-time measurements of materials. Several important characteristics of the hydrogel can be obtained using instrumented indentation. However, the instrumented indentation was not commonly used for hydrogels due to the limitations of commercial instruments which were originally developed for stiff, engineering materials [52]. In addition, the jelly characteristic of these materials leads to a significant effect on adhesion between the indenter tip and the sample, resulting in large errors for any known mathematical correction model [53, 54].

The adhesion of a hydrogel surface attracts the indenter tip and results in a negative load at the beginning of the experiment measured by the indentation machine. It is important to define the initial point of contact of the indenter tip because such point is important for calculating the contact area and the elastic modulus [55], and error in the initial point of contact can lead to inaccurate values by the equipment.

Recent advances [53, 56] show promising results and correct values for measuring the mechanical properties of hydrogels in the range of nanoscale. Basically, the method uses a model proposed by Johnson-Kendall-Roberts (JKR) that consider the adhesion of the gel surface [57]. This model in the recent years only worked accurately with spherical shapes for nanoindentation of hydrogel samples, but the recent work of Jin C. et al. (2017) recently brought the attention of a possible utilization of the JKR model to Berkovich and flat indenters [54].

However, Wei J. et al. (2016) used a multi-indentation to determine the initial indentation depth for the Oliver-Pharr mathematical method correction; the researchers used multiple indents with determined preloads to find the values of preload and maximum apparent indentation depths so they could calculate the initial true initial indentation depth [58].

6.4 Rheology

Rheology is an important technique of characterization of polymers, which mainly aims to evaluate the flow of materials in liquid as well as semisolid states. The obtained data is fundamental to the behavior of hydrogels (Fig. 5e) in different conditions or external stimuli [18].

Knowledge about the viscoelasticity of a hydrogel or gel has great importance for the understanding of the interactions of the polymers used in its production as it is also fundamental to the evaluation of the viability according to its application. Cellulose-based hydrogels may present as a rigid cross-linked gel, with a rubbery consistency, which is optimal for hydrogel application to bone implant or drug delivery systems [59].

The association of cellulose nanofibers with gelatin hydrogels promotes a significant increase of up to 150% in the system's modulus storage, which implies that the cellulose nanofibers provide a viscous consistency to the hydrogels while maintaining the mechanical resistance of the product, a conformability that favors its use, especially as a membrane [24].

Liu et al. (2017) produced dual stimuli-responsive cellulose hydrogel and observed that the elasticity of these hydrogels is influenced by the concentration in the product formulation. A positive relation with this mechanical property is observed; however, this positive relation is only detected until a certain cellulose concentration; after this limit, there is no significant influence [60].

The increase in the mechanical properties of hydrogels is a feature that makes cellulose a biopolymer of choice when the objective is a compound that exhibits viscosity associated with a high elasticity. This characteristic is often associated with the molecular weight of the cellulose [60].

6.4.1 Role of Water in Mechanical Properties of Cellulose Hydrogels Investigated with Rheology

Water is one of the most important components of polysaccharide-based hydrogels (90% of their weight when in their swollen state), and it plays an important role in the mechanical properties of polysaccharide hydrogels. The water inside a hydrogel can bound or semi-bound with the polymer structure; this is important because it forms a hydrogen bond and it is a key role in mechanical properties [61]. Although, these polysaccharides hydrogels can be squeezed through the needle of a syringe, also called "injectable hydrogels"; researchers [62, 63] have analyzed that the squeeze of a needle could change the mechanical properties of this polymer [64, 65].

As such, researchers have been trying to understand the role of water in the mechanical properties of polysaccharide hydrogels; Pasqui et al. (2012) found that in rheology, values of storage modulus (G') and elastic modulus (G'') reduce after these hydrogels are squeezed through a syringe or stressed prior the test but more cycles of stress or passing through a syringe do not vary the values.

The stress performed by the rheometer machine with a raw hydrogel also changes the values of the modulus in polysaccharide hydrogels, and, if more tests are made after this first attempt, it changes the values but becomes continuous with more tests.

This is related to a recovery effect once the material is subjected to further cycles of stresses [65]. However, the structure or degree of cross-linking of the hydrogel does not alter after being stressed, but the entangled polymer chains unroll when a stress occurs and aligns toward the direction of the stress, leading to a swelling by more than 92% of the native cellulose hydrogel due to the free unprotonated COO^- which increases the electrostatic repulsions between the polymer chains.

6.5 Dynamic Mechanical Analysis (DMA)

The dynamical mechanical analysis is an important characterization tool which provides important data about the mechanical and viscoelastic properties of hydrogels, a sinusoidal stress is applied, and the strain of the material is measured (Fig. 5f). This tool can still simulate predetermined conditions, such as the physiological conditions of the human body, and is able to obtain behavioral data and responses of hydrogels on these conditions [66].

The choice of the polymer for hydrogel formulation should take into account several factors, including the objective of using the hydrogel. Since the properties of the hydrogels are directly related to the polymers used in the production, among them the mechanical characteristics which can be influenced, and thus manipulated, according to the concentration of the polymers used [67].

It is possible through DMA; perform the characterization of mechanical properties of hydrogels on different external conditions, such as simulating adverse situations and evaluating the response of these polymers to these stimuli. Cellulose-based hydrogels exhibit excellent mechanical properties, even under conditions of high humidity, while maintaining elasticity with a high tensile modulus [68]. The addition of cellulose nanocrystals to the hydrogel formulation promoted an increase in the stiffness; this property of the cellulose biopolymer is also reported in several other characterization techniques; this is probably due to the cellulose inducing an effect on reinforcement and, more importantly, via DMA. Through the DMA, it was possible to observe that cellulose concentration in a hydrogel containing hyaluronic acid and cellulose nanocrystals promotes a direct positive effect on the stiffness and can promote up to 135% increase over the modulus storage; however, this positive effect is limited to a critical quantity to the cellulose concentration [66].

Basu et al. (2017) demonstrated that hydrogels based on bacterial cellulose have a significant increase in its mechanical stability; this is probably due to the strong hydrogen bond interactions between the cellulose chains [59]. This is also observed with cellulose biopolymers as shown by Lavoratti et al. (2016), where it was used an unsaturated polyester resin (UPR) and cellulose nanofibers (CNFs) obtained from dry cellulose waste of softwood (*Pinus* sp.) and hardwood (*Eucalyptus* sp.); a significant increase occurs in viscoelasticity and the activation energy, which corresponds to the amount of energy required to initiate the mobility of the polymer chains. The study suggests that a better fiber/matrix interface due to cellulose biopolymer promotes a better interaction between the hydrogel [69].

7 Thermal Methods of Analysis

The state of water in hydrogels gives valuable information about their properties. Melting, crystallization, and glass transition temperatures of water in hydrogels reflect the state of the water-polymer interaction and can further improve the understanding of the hydrogel mechanism.

7.1 Differential Scanning Calorimetry (DSC)

Differential scanning calorimetry (DSC) independently measures the rate of heat flow to a substance and its reference material at the same temperature. Heat flow ismonitored and recorded as a function of temperature from which data is derived. Through the application of heat to the system, the properties of the substances are measured by thermal analytical methods.

DSC technique is mainly used to characterize the behavior of different polymers, and their associations in relation to structure and consistency when subjected to temperature variations, either as heating or cooling the sample [5]. DSC can also be used to assess thermal stability with respect to degradation at body temperature and provide a thermal characterization of the materials used to produce hydrogels.

The characterization of hydrogels using DSC can evidence the response to the change in the physical state of the polymer against different temperature conditions. This behavior plays an important role in the indication of the hydrogel usage, which makes it preferable to use as a basis or combination with the formulation, for polymers that promote a certain thermal stability [68].

Cellulose biopolymers incorporated into polyvinyl alcohol fibers have the feature of promoting thermal stability. This ability is due to the property of acting as structural reinforcement the polymer chains of the hydrogels, reflecting an increase of the thermal and mechanical properties of the system [68].

By using heating and cooling cycles in methylcellulose hydrogels, it can be seen from the DSC that gelation rate tends to rise, probably due to the cooperation of the hydrophobic interaction among methyl groups with the intermolecular hydrogen bonds among of hydroxyl groups [70].

Patchan et al. (2013) tested different microcrystalline cellulose derived from various sources and noticed on DSC that cellulose increases the thermal degradation to 250 °C, due to the high melting point of the cellulose. The low-temperature peak position increases with cellulose concentration, possibly because of the high level of linked water in hydrogels with increasing concentration [71].

Barros et al. (2015) investigated a polymer composed of chitosan and (hydroxypropyl)methyl cellulose and report that the cellulose presents thermal resistance and stability to the external stimuli like temperature and pH, without significant alterations in the thermal behavior of these products after variations of pH and temperature [72].

Despite the stability promoted by cellulose against some external stimuli, hydrogels based on this biopolymer can suffer a decrease in the thermal and mechanical

characteristics after their degradation. As indicated by the work of Demitri et al. (2016), this decrease was due to the hydrolysis of the glycosidic bonds of the polymers, causing a partial degradation of the hydrogel [15].

7.2 Thermal Mechanical Analysis (TMA)

The thermomechanical analysis or TMA consists in a technique of characterization of polymers that seeks to determine the thermal stability of these products, obtaining important data regarding the behavior and durability of the polymers in front of different temperature conditions [59].

Cellulose type I and II nanofiber supports high temperatures before starting its degradation process, which occurs from 150 ° C, initially occurring a mild degradation up to 250 °C; above this, it is observed the complete degradation of the cellulose due to the breaking down of its molecular structure. These thermal properties can be altered according to the variation of the biopolymer, where the cellulose nanocrystals have a higher thermal resistance, being degraded at temperatures of approximately 350 °C [73].

The use of cellulose nanowhiskers in the poly(lactide) (PLA) via graft method using n-octadecyl-isocyanate provides an increase in the resistance and thermal stability which is greatly influenced by the concentration used. However, the concentrations that increased the thermal characteristics of the product were the same ones that allowed a reinforcement action in the hydrogel network [74].

A comparison of the thermal stability between the natural fiber cellulose biopolymers with nanocrystals formed from mercerized fibers reveals that the latter has a higher stability against temperature changes; this is due to the stronger hydrogen bonds; another factor that contributes to this is the high purity and crystallinity of the cellulose nanocrystals [74].

A data that can be obtained through the TMA is the coefficient of thermal expansion (CTE); this is an important thermophysical property for polymers, mainly thermosetting resins, where the lower the CTE, the greater the dimensional stability of the polymer or hydrogel. Due to better dispersion and morphology of cellulose fibers, hydrogels formulated with these polymers have a lower CTE and also influence other thermophysical aspects such as a better thermal stability of the product [69].

8 Biological Techniques

Cellulose hydrogels have many applications in biomedicine. However, it is important to analyze its biocompatibility including cytotoxicity and how cells proliferate and differentiate into these structures for further studies in vivo. This section introduces some basic concepts of biological techniques and the behavior of cellulose hydrogels.

8.1 Cell Culture and Adhesion

The ability of a hydrogel to maintain cell adhesion and proliferation on its surface as well as control its behavior is essential requirements for the successful use of these hydrogels in the field of tissue engineering [66].

The addition of cellulose nanocrystals in hyaluronic acid hydrogels has shown good interaction with cells. The cultures of adipose cells in these materials have shown proliferation and elongation after 24 h of culture. The study suggests that presence of cellulose nanocrystals corresponds with the density, morphology, and cytoskeleton organization of the studied cells [66].

Hossain et al. (2014) studied PLA fibers coated with blends of cellulose nanowhiskers compared to uncoated PLA fibers. The results have shown that hydrogels based on cellulose nanowhiskers present an excellent environment for cell adhesion and proliferation, which occurs intensely and rapidly. In addition, after 24 h of cell culture, it was possible to observe the formation of a confluent structure with several cell layers, which suggests a cellulose stimulus for cell attachment as observed in Fig. 8 [75].

When performing cell culture derived from bone marrow in a PEGDA700 hydrogel incorporated with CMCNa porous implant. The interaction observed is that these hydrogels act to stimulate cell adhesion and proliferation, with intense cell growth being observed at 14 days. In addition, during this period, an increase in cell differentiation and activity of osteoblasts occurs on samples with cellulose. This confirms the ability of the cellulose-based implant to withstand osteoblast differentiation [15].

Raucci et al. (2014) studied hydroxyl ethyl cellulose (HEC) incorporated with CMCNa using a chemical treatment that induces –COOH functional groups and

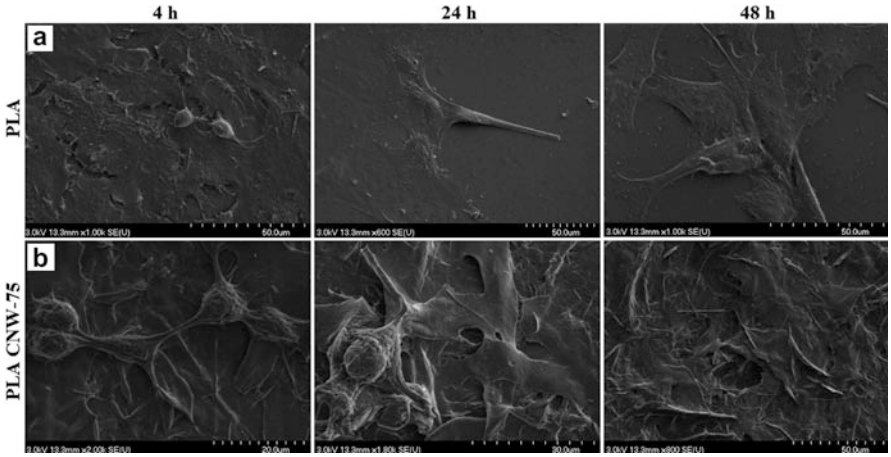

Fig. 8 NIH-3 T3 mouse fibroblast cell morphology and spreading at varying time points (4, 24, and 48 h). (**a**) Polylactic acid; (**b**) polylactic acid with cellulose nanowhiskers. (Reprinted with permission from [75]. Copyright © 2017, ACS)

investigated this hydrogel using human mesenchymal stem cells line (hMSC). The results show that the cellulose hydrogel exhibits its potential to be used as implants or biological membranes, which have excellent biocompatibility for the most diverse tissues that make up living organisms. In addition, low cytotoxicity was detected which allowed the adhesion of these cells on hydrogels with rapid and intense cellular development on its surface compared to standard samples [76].

8.1.1 3-(4, 5-Dimethylthiazol-2-Yl)-2, 5-Diphenyltetrazolium Bromide (MTT) Assay

The MTT (3-(4, 5-dimethylthiazol-2-YI)-2, 5-diphenyltetrazolium bromide) assessment seeks to analyze the viability of cultured cells in hydrogels by adding information on the cell functionality effect. The test provides fundamental data for the biocompatibility and the application of polymers or hydrogels that are aimed to be used as biomaterials, such as implants that promote the acceleration of tissue healing [77].

Peng et al. (2016) investigated a novel quaternized cellulose (QC) and native cellulose in NaOH/urea aqueous solution. These hydrogels present excellent biological characteristics, besides allowing excellent cell adhesion and proliferation. The cellulose-based hydrogels have low cytotoxicity, where MTT assays exhibited that up to 80% of the cell growth remained viable, mainly due to the improvement of the hydrogel cytocompatibility due to the cellulose network [77, 78].

The cytotoxicity of the cellulose biopolymer in various cells has already been reported in literature [79]; these properties favor the use of this biopolymer in the biomedical area, artificial blood vessels [80], implants for bone tissue [25], drug delivery system [81], and application in the regeneration of peripheral nerve damage [82].

Such improved biocompatibility is shown in Fig. 9 where work of Cheng et al. (2014) investigated a thermoresponsive polysaccharide hydrogel based on nanofibrous cellulose and elastin-like polypeptide (ELP). High fibroblast viability was obtained (Fig. 9a), indicating a non-cytotoxic hydrogel while cells were spread toward the surface of the hydrogel (Fig. 9b), and they were capable of proliferating even after 7 days of incubation (Fig. 9c, d).

8.2 In Vivo Characterization

For hydrogels designed for biomedical applications, in vivo biological characterization tests are fundamental; through this analysis it is possible to evaluate the behavior of the hydrogel, either as a controlled drug distribution system or as implants for tissue replacement or regeneration, on the conditions of living organisms [84].

Cellulose-based hydrogels are widely studied and employed in the biomedical area for various purposes such as wound dressing, which is one of the most reported, and its use has been researched for some time with the aim of treating wounds by burns and chronic injuries that are difficult to heal [84].

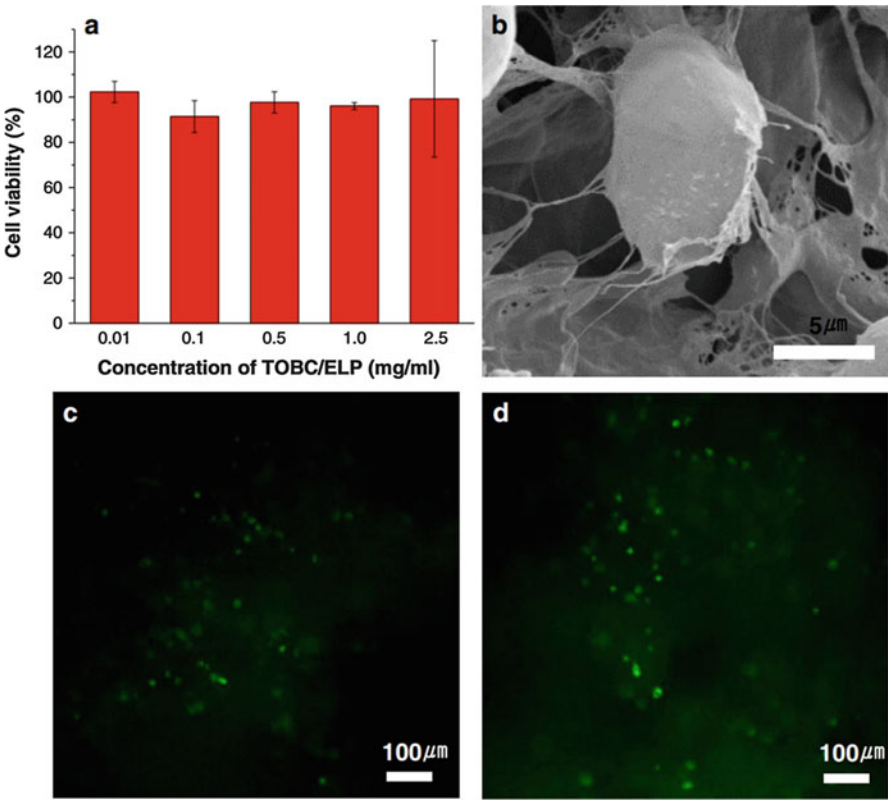

Fig. 9 (**a**) MTT results of the TOBC/ELP solution. (**b**) FESEM micrographs of cells encapsulated in a TOBC/ELP hydrogel. Fluorescence microscopic images of fibroblast cells encapsulated in a TOBC/ELP hydrogel after (**c**) 1 day and (**d**) 7 days of incubation (cells were live/dead stained). (Reprinted with permission from [83]. Copyright © 2017, Springer)

Portal et al. (2009) investigated the use of cellulose membranes for the application of healing chronic skin wounds, which are difficult to heal. The results suggest that cellulose membranes healed 75% of analyzed wounds in 81 days, while conventional treatment took 315 days to heal 75% of the wounds. The study also evidences on cellulose membranes, a reduction in wound epithelization time of 74.5% when compared to conventional treatment. This indicates that cellulose on implants clearly benefits for the treatment of chronic injuries [85].

The elasticity and conformability present in implants made from cellulose lead these materials to obtain excellent adhesion, favoring their application in practically any part of the body. The use as a wound dressing for burn wounds in the face promotes a complete healing of wounds in 44 days, making it not necessary to use grafts as well as not being observed signs of extensive scars [86]. Cellulose membranes also have adequate properties on mechanical and biological for wound dressing. These membranes act as an accelerating factor in the healing of wounds,

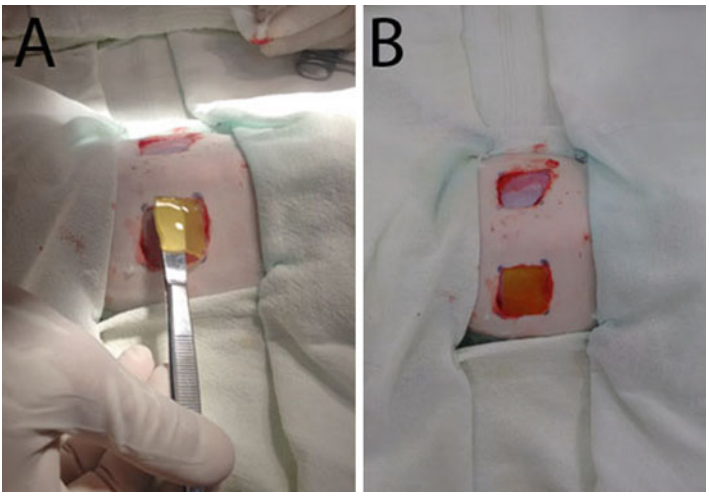

Fig. 10 (**a**) Placement of hydrogel membrane in the surgical wound; (**b**) hydrogel dressing in the target of wound. (Original artwork)

presenting ease of application and removal of the wounds while also being a painless product [87]. A cellulose membrane for wound healing being tested in vivo is shown in Fig. 10, and, due to the swelling characteristics of these hydrogels, it creates a moist environment hydrating the wound while also relieving the pain by delivering any drugs that can be introduced in its structure.

Cellulose membranes also work well in wounds that are difficult to heal, such as wounds in patients with diabetes, and an increase in wound healing rate has been reported as well as a reduction in the epithelization in wound healing time of these patients when compared to other treatment methods [88].

The use of a cellulose-based biosynthetic blood vessel as an implant in an ovine animal model revealed promising results; this cellulose implant could function even after 13 months, with the presence of endothelial cellularity in all segments of the implant [80].

9 Conclusion

The cellulose biopolymer is a material that presents wide versatility of use in several areas, is a renewable resource, and is present abundantly in nature which has properties that favor its use for various purposes.

The hydrogels based on, or associated with, cellulose has a higher capacity to withstand mechanical forces, maintaining a balance between stiffness and elasticity, besides increasing thermal resistance and to other external stimuli. Finally, this biopolymer has excellent biocompatibility and ability to maintain a favorable environment for cell growth and proliferation.

The characterization techniques allow evaluating the addition and permanence of all the positive properties of biopolymers as cellulose hydrogels. These techniques are essential for the research and production of increasingly improved and specialized hydrogels for a specific application.

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Morphological Characterization of Hydrogels

26

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Contents

Abstract

Hydrogels are physically or chemically cross-linked polymer networks that are able to absorb large amounts of water. They can be classified into different categories depending on various parameters including the preparation method, the charge, and the mechanical and structural characteristics. The morphological

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structures are differed from hydrogel compositions to preparation method, fabrication techniques, type of hydrophobic substitutes, etc. This chapter addresses an overview of the morphological characterization of hydrogels and impact of these properties in various potential applications of hydrogels. In a first part, morphological characterizations of hydrogels directly prepared from native materials are described. In a second part, morphological characterizations of hydrogels prepared from different derivatives of native materials by physical as well as chemical cross-linking strategies are introduced. In a third part, morphological characterizations of composite type hydrogels including blending composites, polyelectrolyte complexes, and interpenetrating polymer networks (IPNs) are discussed. In a final part, morphological characterizations of inorganic nanoparticles incorporated hybrid hydrogels are described.

Keywords
Superabsorbent hydrogels · Hydrogel's morphology · Hybrid hydrogel · Cellulose

1 Introduction

Hydrogel is an insoluble polymeric substance that shows the ability to swell and preserve substantial amount of water in its three-dimensional network [1]. In a different way, hydrogels are explained as polymeric arrangements those exhibit the capability of swelling in water and holding a considerable portion of water (>20%) in their 3D structure, without dissolving in water [2]. Sometimes, to describe the polymeric cross-linked network, the hydrogels and gels are used interchangeably by the biomaterial scientists. Actually whether they are gels or hydrogels depend on their fluidity in steady-state, where the gels are more dilute cross-linked system than hydrogels [3]. This cross-linking is responsible for their insolubility in water because of the ionic interaction and hydrogen bonding [4], and this degree of cross-linking in hydrogels generally determines their mechanical strength and physical integrity [5].

There are numerous ways to classify hydrogels. Nowadays, classification based on physical properties has drawn more importance due to their extensive uses in diversified fields and exclusive characteristics, such as capacity of diffusion and swelling. Based on their physical properties and mode of applications, hydrogels can be classified into three ways, namely, solid, semisolid, and liquids [6]. Nevertheless, as they are fundamentally made of cross-linking network, based on hydrogels' cross-linking, they can be classified into two groups: (a) physically cross-linked or self-assembled hydrogel and (b) chemically cross-linked hydrogel [7]. In the category of physically cross-linked or self-assembled hydrogel preparation, various methods have been reported by various researchers, such as freeze-thawing [8], stereo complex formation (dissolving each product in water and mixing the solution) [9], ionic interaction (addition of di- or trivalent counter ions result in hydrogel systems) [10], hydrogen bonding interactions [11], and maturation (heat-induced

aggregation) [12]. On the other hand, chemically cross-linked hydrogel preparations have been documented numerous testimonies, such as chemical cross-linking [13], chemical grafting [14], radiation grafting [15], radical polymerization [16], condensation reaction [17], enzymatic reaction [18], and high-energy radiation [19].

Due to hydrogels mechanical strength, physical integrity, biocompatibility, degradability, functionality, flexibility, and adaptability, they have achieved extraordinary appreciation in various fields of engineering and technology. Mentionable sites of their applications are tissue engineering [20], therapeutic applications [21], drug delivery [22], cartilage tissue, soft tissue engineering, cell scaffold, regenerative medicine and cartilage repair [23], agricultural and horticultural engineering [24], water purification [25], antimicrobials [26], and bio catalysis [27].

The water sorption ability and swelling kinetics of a hydrogel depend on its porosity. Therefore, increment of porosity in hydrogels is regarded as the most important issue to most researchers. It can be achieved in hydrogels either by physical or chemical techniques. The chemical techniques may encompass phase-separation, foaming, lyophilization, solvent casting, particulate-leaching, etc. [28], while the physical techniques may include laser sintering [29] and laser-enhanced surface modification [30]. To portray a complete picture of surface morphology and topography of numerous hydrogels is the prime target of this chapter. With this aim, scanning electron microscopy (SEM), laser scanning confocal microscopy (LSCM), and atomic force microscopy (AFM) of several types of hydrogels are elucidated comprehensively.

2 Morphological Characterization of Cellulose-Based Hydrogel

Hydrogels, a three-dimensional polymer network able to absorb and release large amount of water without dissolution in a reversible manner, has become a behemoth in research field owing to its versatility in application ranging from agricultural water conservation [31] to cancer drug delivery system [32]. Though most of the hydrogels prepared are from synthetic polymers such as those formed by cross-linking poly (vinyl alcohol) [33], poly (*N*-isopropylacrylamide) [34], poly (acrylic acid) [35], poly (amido-amine) [36], poly(ethylene glycol) [37], and polyacrylamide [38], in recent times, natural polymers, mainly cellulose-based hydrogels, have attracted major attention due to their biocompatibility, biodegradability, and low toxicity.

Cellulose, the most abundant natural polymer, has become an enticing proposition as the base material to develop hydrogels. Because of its biocompatibility and inexhaustible nature, cellulose and cellulose-based hydrogels have been unequivocally used in wide range of applications. Cellulose, due to the presence of hydroxyl groups in the structure, offers an easier way of functionalization which leads to formation of so many cellulose-based derivatives. Hydrogels prepared from cellulose and cellulose derivatives can be modified to meet the demands of diversified product demand [39].

Morphological properties of cellulose-based hydrogels are analyzed by scanning electron microscope (SEM). SEM reveals the porosity and nature of hydrogel

structure. Moreover, the effect of modification on the size of the pore is divulged by SEM images. SEM sample is generally prepared by first swelling the hydrogels, then freezing in liquid nitrogen, and finally freeze-drying and sputtering with gold prior to the SEM observation [40, 41]. Atomic force microscope (AFM) helps to evaluate the topological attributes of the hydrogels, where AFM discloses the uniformity of surface roughness of the hydrogels [42].

2.1 Native Cellulose-Based Hydrogel

Native cellulose-based hydrogels, owing to the presence of many hydroxyl groups, have been prepared through physical cross-linking. One such native cellulose-based hydrogel was prepared by adding a cross-linking agent in cellulose solution. NaOH-urea was used as the solvent to dissolve cellulose for the preparation of cellulose hydrogel with epichlorohydrin as a cross-linker. This was a "one-step" method which used unsubstituted cellulose [43]. Two different posttreatment methods were compared in morphological characterization. One was heating treatment, and the other one was freezing treatment [43].

From Fig. 1, it is clear that the heating posttreatment creates a macroporous inner structure. Moreover, the pore size decreases with increasing cellulose concentration.

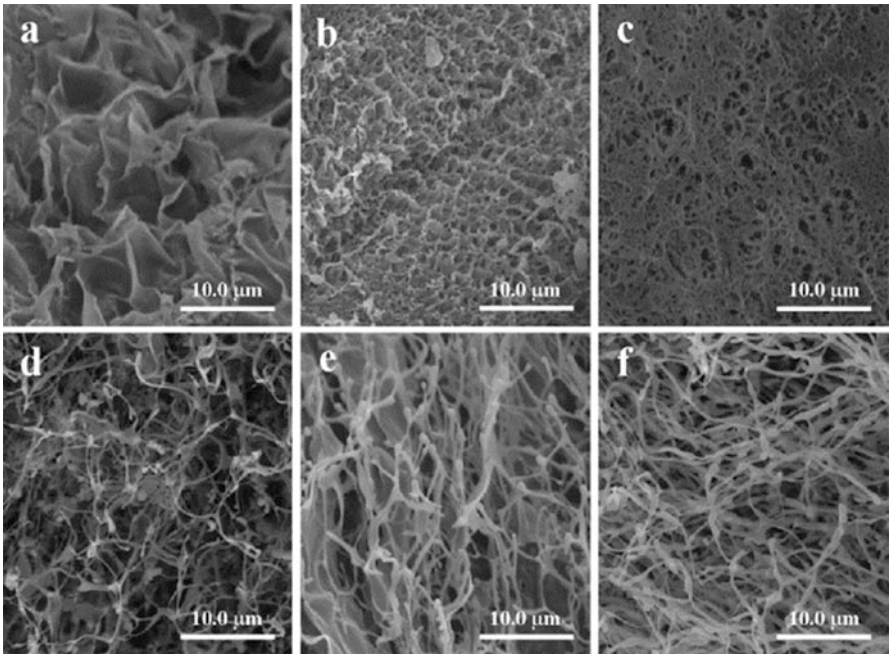

Fig. 1 SEM images of cellulose hydrogels developed by heating (top) and freezing (bottom) posttreatment with varying cellulose content: (**a**) 2 wt.%, (**b**) 3 wt.%, (**c**) 4 wt.%, (**d**) 2 wt.%, (**e**) 3 wt.%, (**f**) 4 wt.%. (Reprinted with permission from [43] Copyright © 2010 Elsevier)

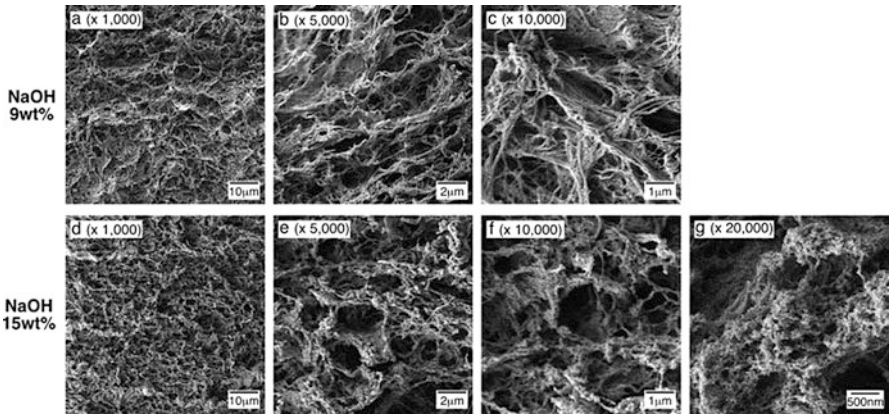

Fig. 2 SEM images of freeze-dried hydrogels prepared by 9 wt.% NaOH (**a**–**c**) and 15 wt.% NaOH (**d**–**g**). (Reprinted with permission from [44] Copyright © 2011, Elsevier)

On the other hand, hydrogels prepared by freezing treatment display a fiber-like structure, a significant difference from heating treatment. The reason behind this clear difference in structure is probably slow and strong self-association of cellulose chain at lower temperature.

Kentaro et al. reported fabrication of hydrogel from cellulose nanofibers by single alkaline treatment only. There was morphological difference in hydrogels prepared by this method depending on the concentration of alkali used [44].

From Fig. 2, both type of hydrogels exhibited similar network structures with micro- and nanopores when observed at 1000× magnification. But observation at higher magnification revealed morphological differences between the two types of hydrogels. Hydrogels prepared by 9 wt.% NaOH demonstrated a network that was formed by aggregation of individual cellulose nanofibers (Fig. 2b and c) [45], while hydrogels prepared by 15 wt.% NaOH showed a sponge-like network structure due to coalescence of the kinky nanofibers (Fig. 2e–g).

2.2 Cellulose Derivative-Based Hydrogel

Biocompatible cellulose derivatives, such as carboxymethyl cellulose, hydroxyethyl cellulose, methyl cellulose, and cellulose acetoacetate, have become an important competent in hydrogel fabrication. These hydrogels can be formed through physical-linking or chemical cross-linking [46, 47].

A superabsorbent hydrogel was prepared from hydroxyethyl cellulose (HEC), a cellulose derivative, and acrylic acid (AAc) by radiation-initiated cross-linking in aqueous solution [48]. Hydroxyethyl cellulose (HEC), one of the most widely used cellulose derivatives, is known for its application as a stabilizer, coating agent, or thickener. Recently, it has generated interest in hydrogel synthesis. For modifying gel properties, a second polymer was introduced in the hydrogel system. Acrylic acid

(AAc), a polymer with low cytotoxicity and good swelling properties, was incorporated into the hydrogel to improve gel properties [49]. HEC of three different molar masses such as $M_v = 90{,}000$ named HEC90, $M_v = 720{,}000$ named HEC720, and $M_v = 1{,}300{,}000$ named HEC1300 were used [48].

SEM images from Fig. 3 show the effect of partial replacement of HEC with AAc. Highly porous structure with large pores was visible on the surface of HEC90/AAc gels. Though the surface was smooth in hydrogels with 10% AAc (Fig. 3b), increasing AAc concentration brought heterogeneity on the pore surface, which resulted in granule like structure. This trend was more highlighted as concentration of AAc was increased to 30%. This could be attributed to homopolymerization of acrylic acid which led to less homogeneous gel structure.

On the other hand, HEC1300 gels showed a wide pore size with relatively smaller pores and homogeneous surface (Fig. 3e and f). The difference in pore size between current and previous gel could be due to higher crosslink density leading to substantial lower water uptake before freeze-drying. In HEC1300/AAc gels containing 5% AAc, a denser structure with smaller pores (Fig. 3g and h) can be located owing to the improved gelation in presence of monomer. Here, heterogeneity of the surface is more prominent compared to HEC90/AAc gels. This can be a result of high solution viscosity of high-molecular-mass HEC. As the mobility of acrylic acid is less impeded by the increased viscosity than the large polymer chains, homopolymerization becomes dominant which leads to rough network surface. High AAc content has no substantial effect on the gel properties, but it does impact homogeneity negatively [48].

Hongchen et al. reported a cellulose derivative-based smart hydrogel by combining cellulose acetoacetate (CAA) and cystamine dihydrochloride (CYS). This hydrogel exhibited good response to both pH and redox triggers [50]. Stimuli-responsive hydrogels have become a new avenue of research because of their potential application in sensing [51], cell culture [52], drug release [53], tissue scaffolding [54], and 3D printing [55]. Smart responsive hydrogels are capable of changing their size and shape in response to environmental stimuli such as temperature [56], enzymes [57], pH [58], light [59], and electric and magnetic field [60]. The pH/redox dual-responsive cellulose hydrogels prepared from CAA and CYS combined a pH responsive dynamic covalent enamine moiety and a redox-sensitive disulfide moiety [61, 62]. They demonstrated capacity to work in physiological conditions which opens up possible application as smart sensors and targeted drug release.

SEM images were investigated to test morphological change of the hydrogel under physiological condition such as in phosphate-buffered saline (PBS) solution (pH = 7.4).

From Fig. 4, it is clear that the prepared hydrogels (Fig. 4a) have honeycomb-like macroporous structure which is significant for biomedical application due to its capacity to facilitate drug loading and release, also offering void space for oxygen and nutrient transportation and cell proliferation [63]. This structure is consistent (Fig. 4b) in same pH, but when pH is decreased to 3.5 (Fig. 4c), an irregular deformed morphology is apparent. This is due to the fact that under acidic condition, the intermolecular enamine bonds, main protagonist in determining gel stability, were hydrolyzed to amine and acetoacetyl groups.

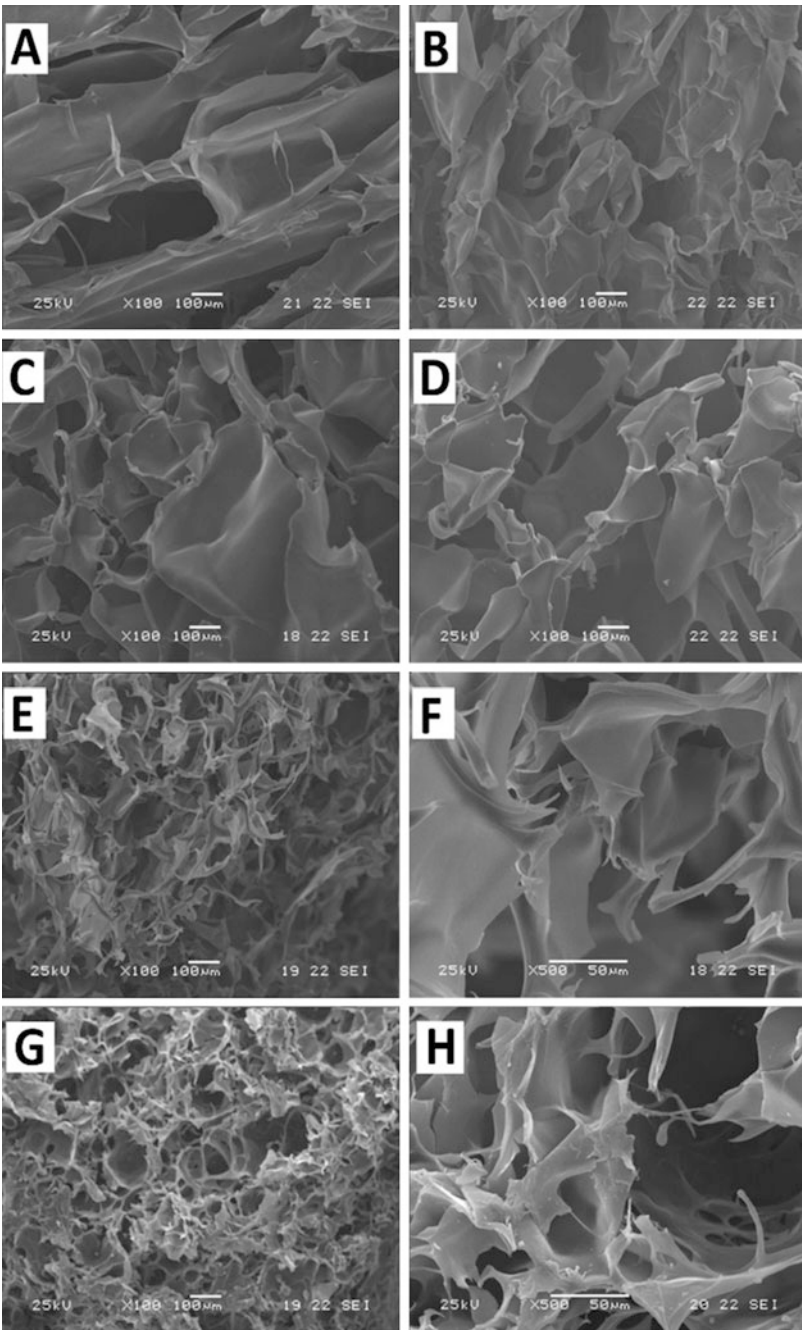

Fig. 3 SEM images of HEC90/AAc hydrogel with 5% (**a**), 10% (**b**), 20% (**c**), and 30% (**d**) AAc, pure HEC1300 (**e** and **f**) and HEC1300/AAc hydrogel with 5% AAc (**g** and **h**). Magnification: ×100 (**a**–**e**, **g**) and ×500 (**f**, **h**). (Reprinted with permission from [48] Copyright © 2017, Elsevier)

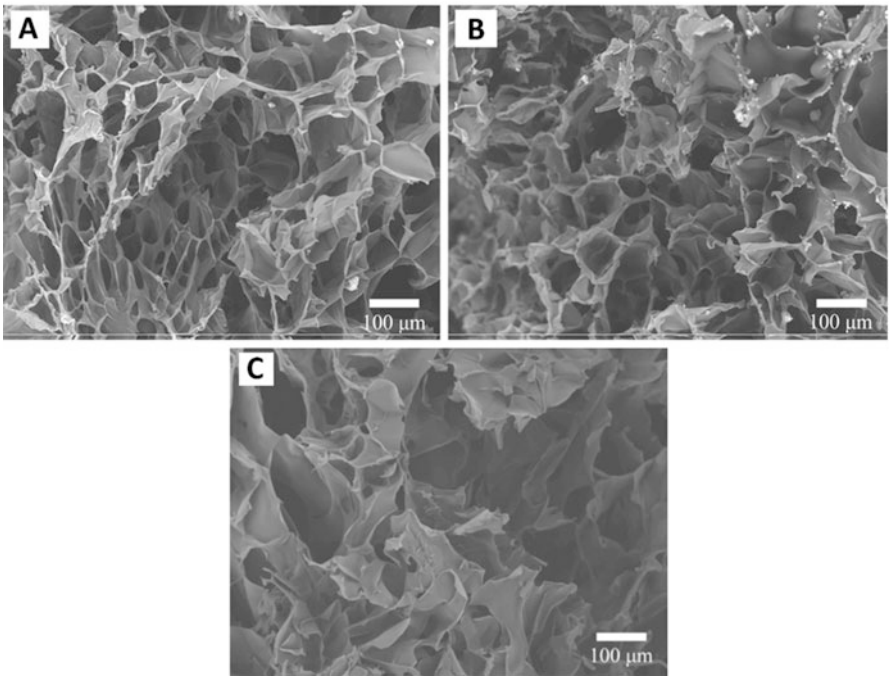

Fig. 4 (**a**) SEM image of the prepared hydrogel (2% CAA, 10% CYS) at pH 7.4, (**b**) SEM image of the prepared hydrogel (2% CAA, 10% CYS) immersed in pH 7.4 buffer after 72 h, (**c**) SEM image of the prepared hydrogel (2% CAA, 10% CYS) immersed in pH 3.5 buffer after 72 h. (Reprinted with permission from [50] Copyright © 2017, Elsevier)

Jiaojiao et al. fabricated a stimuli responsive hydrogel, prepared from hydroxyethyl cellulose and lignosulfonate-graft-poly (acrylic acid), having semi-interpenetrating network (semi-IPN) structure [64]. Lignin, the second most abundant natural polymer after cellulose, is generated in large amount during pulping process all over the world [65–67]. Lignosulfonate (LS), generally treated as a waste product in pulping industry, offers sufficient reactant functional groups to make it an attractive component in different applications [68–70]. Hydroxyethyl cellulose (HEC), a hydrogen-bond acceptor, was combined with acrylic acid (AAc), a hydrogen bond donor, and lignosulfonate in HEC solution by in situ polymerization. These hydrogels exhibited good mechanical properties and stimuli-responsive swelling properties which can open door for many potential new applications [64].

From Fig. 5, hydrogel containing no lignosulfonate shows less homogenous structure with nonporous region (Fig. 5a). Compared to this, hydrogel with 7% lignosulfonate content exhibits a highly porous honeycomb-type structure with regular pores having 11.2 micrometer average diameter. These pores form capillary channels, which leads to high accessibility of water to the amorphous region of the hydrogel giving it as high as 85% water absorption capacity [71]. So, the morphological changes on the hydrogel have significant effect on its application as superabsorbent [64].

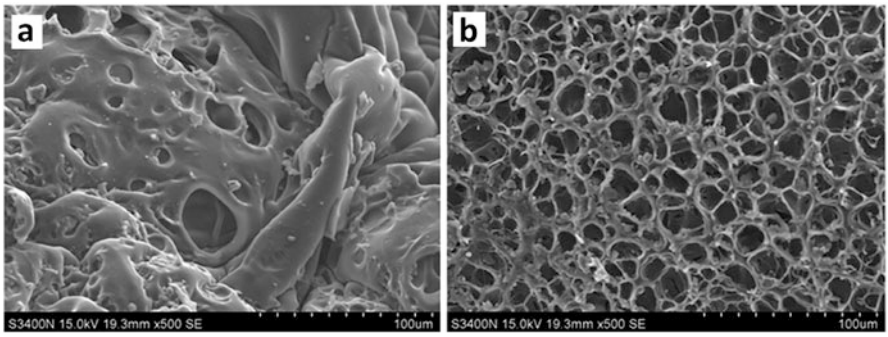

Fig. 5 SEM images of (**a**) LS-AA/HEC hydrogel with 0% LS; (**b**) LS-AA/HEC hydrogel with 7% LS. (Reprinted with permission from [64] Copyright © 2017, Elsevier)

2.3 Cellulose-Biopolymer Composite Hydrogel

Cellulose and different biopolymers, such as gelatin, alginate, starch, and hyaluronate, have been blended to fabricate hydrogels with excellent properties applicable in various applications. Treesuppharat et al. successfully combined bacterial cellulose with gelatin to prepare hydrogel composite material useful in drug delivery systems [42]. Gelatin, owing to its attractive properties like high water absorption, non-toxicity, and biodegradability, has become a notable contender in biopolymer-based hydrogels fabrication intended to be used in drug delivery systems [72–74]. Bacterial cellulose, one of the most effective reinforcement materials, has structure similar to plant-based cellulose but offers added advantages such as high specific surface area, high degree of polymerization, and high crystallinity. Presence of bacterial cellulose in cellulose-gelatin hydrogel imparts tensile strength and dimensional stability when put under externally applied forces [75, 76].

From Fig. 6, pure gelatin and bacterial cellulose-gelatin hydrogel both exhibit porous structure due to removal of solvent. The pores have spherical shape in general and no specific size. Importantly, the size of the pores decreased as the amount of gelation in the hydrogel was decreased. So morphological properties was affected by the ratio of gelatin and bacterial cellulose [42].

From Fig. 7, topology of gelatin and bacterial cellulose-gelatin hydrogel was analyzed, and it revealed uniformity of surface roughness. It is clear that bacterial cellulose has higher degree of roughness. But in hydrogels, bacterial cellulose entered the cavities of gelatin and exhibited increased smoothness. Consequently, both SEM and AFM images disclosed the morphological change with decreasing gelatin percentage in hydrogel [42].

Linseed gum-cellulose hydrogels were developed by mixing cellulose and linseed gum in NaOH/urea solvent and epichlorohydrin was used as cross-linking agent [31]. This hydrogel was prepared with water conservation as the intended application, as linseed gum possessed good water retention capability owing to its

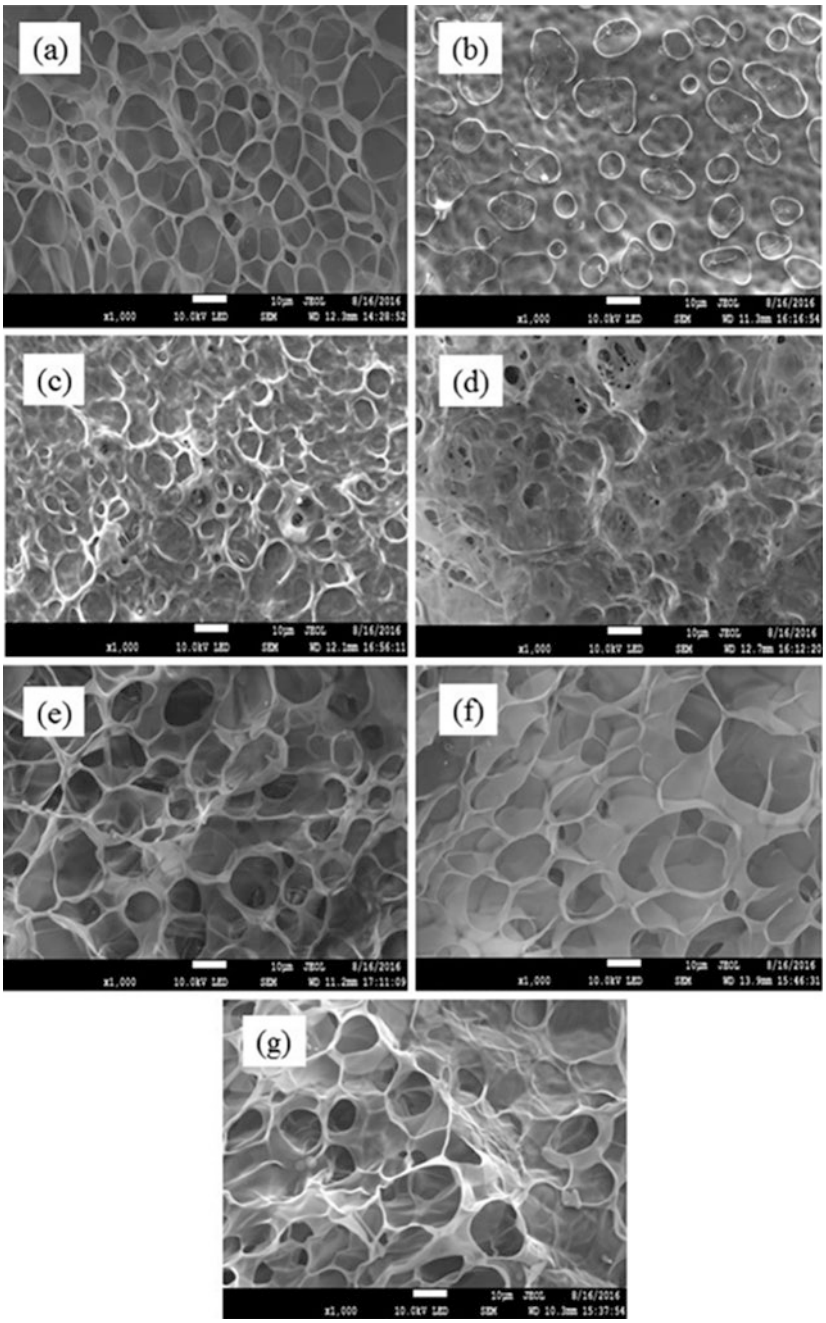

Fig. 6 SEM images of bacterial cellulose and gelatin hydrogels (**a**) pure gelatin and hydrogels with gelatin-to-bacterial cellulose ratios of (**b**) 25:1, (**c**) 50:1, (**d**) 100:1, (**e**) 200:1, (**f**) 300:1, (**g**) 400:1. (Reprinted with permission from [42] Copyright © 2017, Elsevier)

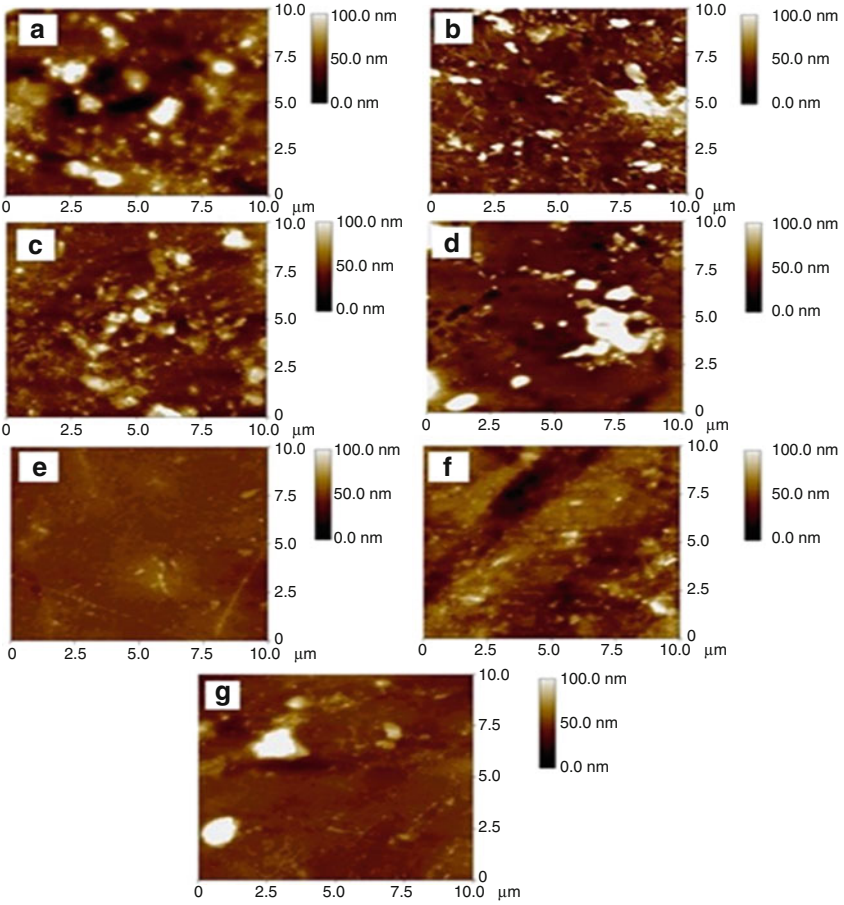

Fig. 7 AFM images in lateral contact mode (AFM scan size 10 µm × 10 µm) of bacterial cellulose and gelatin hydrogels (**a**) pure gelatin and hydrogels with gelatin-to-bacterial cellulose ratios of (**b**) 25:1, (**c**) 50:1, (**d**) 100:1, (**e**) 200:1, (**f**) 300:1, (**g**) 400:1. (Reprinted with permission from [42] Copyright © 2017, Elsevier)

high swelling ratio and viscosity. But as linseed gum exhibits weak gel properties, it was combined with cellulose to impart toughness. Moreover, chlorohydrin was added to bring its superabsorbent property to the fabricated hydrogel [77]. The linseed gum-cellulose composite solutions were prepared by mixing linseed gum (LG) and cellulose (C) solutions with ratio of 4:6, 3:7, 2:8, 1:9, and 0:10 (ratio of solid contents of linseed gum and cellulose) by weight, respectively. The composite hydrogels were named as G1 (LG-C ratio 4:6), G2 (LG-C ratio 3:7), G3 (LG-C ratio 2:8), G4 (LG-C ratio 1:9), and G5 (LG-C ratio 0:10) according to the ratio of linseed gum to cellulose.

From Fig. 8, it is clear that the hydrogels had three-dimensional macroporous inner structures. This porous structure facilitates the permeation of water, which allowed water to penetrate the inner structure. As a result of absorption of water, the space in

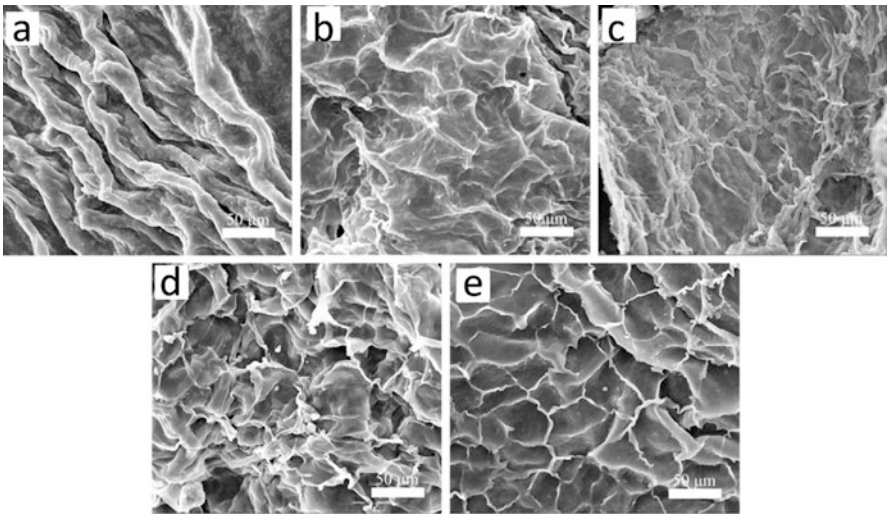

Fig. 8 SEM images (after 7 days water immersion) of hydrogels with different linseed gum ratio: (**a**) G1, (**b**) G2, (**c**) G3, (**d**) G4, and (**e**) G5. (Reprinted with permission from [31] Copyright © 2016, Elsevier)

the networks of hydrogels was increased. This was due to electrostatic repulsion from the anionic groups in linseed gum [78]. The average size of pore increased from 18 to 28 micrometer with increasing gum content in hydrogel, from G4 to G2. This in turn, resulted in higher absorption of water which led to a loose structure. Conversely, the average pore size of G3 and G4 was smaller than G5, which could be attributed to failure of linseed gum to support the hydrogel structure in the same way cellulose does. Consequently, linseed gum contributed to controlling the pore size; on the other hand, cellulose played a role as backbone to strengthen the porous structure [78].

2.4 Cellulose-Inorganic Nanoparticle Hybrid Hydrogel

Cellulose-inorganic nanoparticle hybrid hydrogels have garnered interest due to potential applications in optical, magnetic, electronic, and biomedical fields [79]. Monireh et al. have conducted a study on superabsorbent hydrogel based on carboxymethyl cellulose (CMC) and graphene oxide nanoparticles. This hybrid hydrogel was prepared, with controlled drug delivery as intended application, by physically cross-linking cellulose and graphene oxide nanoparticles with $FeCl_3.6H_2O$. In contrast to pure polymer hydrogels, nanoparticle-incorporated hydrogels exhibited better results owing to their stronger physical, chemical, and biological properties [80, 81]. Graphene oxide (GO), due to biocompatibility, low toxicity, and amphiphilic nature owing to the functional groups such as hydroxyl, epoxide, and carboxyl on the surface, is an attractive candidate in drug delivery

system, which also happens to greatly enhance the mechanical properties of CMC [82–84]. CMC, a biodegradable polymer with multiple carboxyl groups, exhibits good coordination with metal and thus forms excellent hybrid hydrogels [85].

From Fig. 9, it is clear that GO nanosheets are visible (Fig. 9a and b). Pure CMC hydrogel exhibits rough structure and visible wrinkles on the surface (Fig. 9c), while CMC/GO hydrogel containing GO has smooth surface due to cross-linking effect of intercalated GO sheets (Fig. 9d–f). These sheets make strong H-bonding interaction with functional group of CMC, thus increasing smoothness of the surface [32].

Another hybrid hydrogel was prepared from hydroxypropyl cellulose (HPC), a cellulose derivative, and inorganic nanoparticle such as molybdenum disulfide (MoS_2) with intended application as dye absorbent [86].

Hydroxypropyl cellulose, an important cellulose derivative due to its high water solubility, has been used to remove dyes from aqueous solution [87]. But its relatively low absorption capacity has limited its application as absorbent [88, 89]. To counteract this limitation, incorporation of nanoparticle with large surface area and multiple functional group is often deployed [90, 91]. Moreover, addition of nanoparticle to the hydrogel system improves mechanical properties of cellulose-based hydrogels. Molybdenum disulfide (MoS_2) has been used in the fabrication of hydrogels due to its two-dimensional structure, which is expected to improve

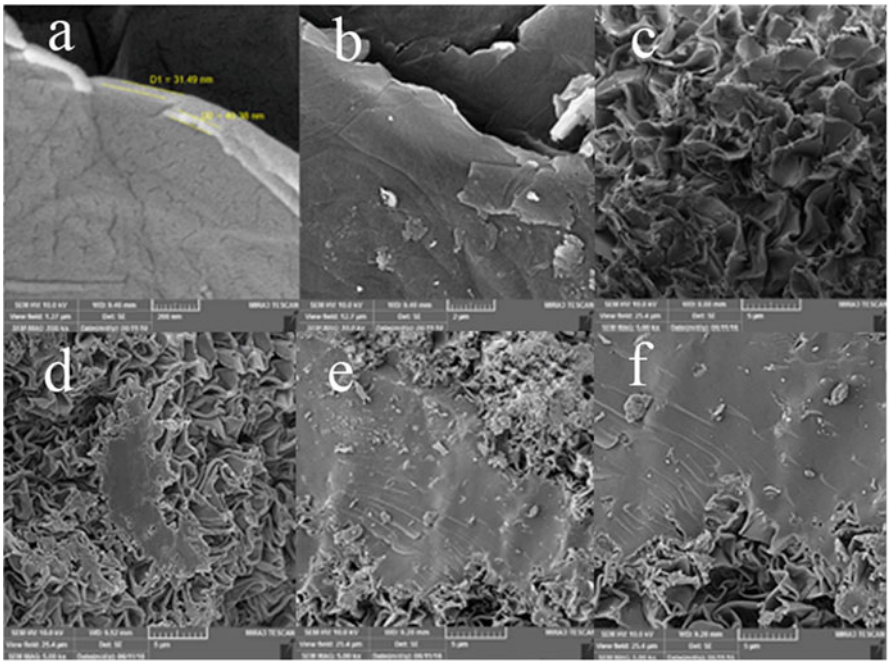

Fig. 9 SEM images of GO (**a** and **b**), CMC hydrogel (**c**) and hybrid hydrogel of CMC/GO with different GO content (**d**-5%, **e**-10%, and **f**-15%). (Reprinted with permission from [32] Copyright © 2017, Elsevier)

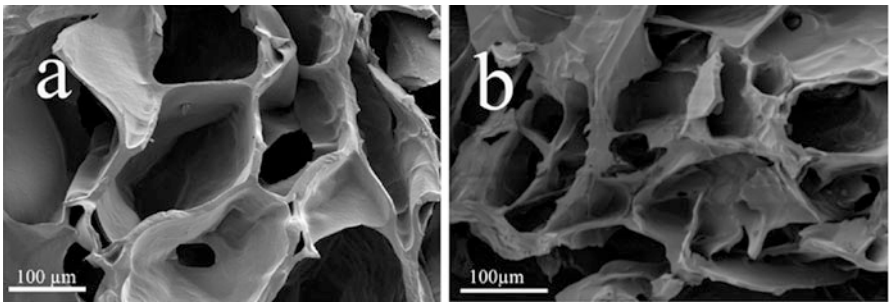

Fig. 10 SEM images of HPC hydrogel (**a**) and MoS_2-HPC/HPC hydrogel (**b**). (Reprinted with permission from [86] Copyright © 2017, Elsevier)

absorption capacity of the hydrogels. In addition to this, MoS_2 has been widely used as photocatalysts, which catalyzes the degradation of organic dyes facilitating its removal from aqueous system [92].

From Fig. 10, SEM image of HPC hydrogel shows a loose 3D network structure of porous nature. This is due to phase-separation upon increasing reaction temperature to 50 °C. While MoS_2/HPC hydrogel shows no distinct MoS_2/HPC nanosheets, which indicates a uniform distribution of MoS_2/HPC nanosheets in HPC [93]. Moreover, a smaller pore size than that of the previous hydrogel was observed as a result of addition of MoS_2/HPC, which might have reduced the expansion of the gel matrix leading to decrease in pore size [41].

3 Morphological Characterization of Chitosan-Based Hydrogels

Chitosan is the deacetylated product of chitin (*N*-acetyl-d-glucosamine) which is the second most abundant natural biopolymers after cellulose. Recently chitosan and chitosan-based hydrogels have gained considerable attention for their unique properties like stability, biocompatibility, stimuli sensitivity, biodegradability, bacteriostatic effects, and mechanical strength to be used in numerous applications like in drug delivery, protein release, tissue engineering, dye removal, wastewater treatment, etc. [94–96].

Chitosan and chitosan-based hydrogels can be prepared by physical, chemical, or radiation-induced cross-linking, and the physical characteristics like pore size, distribution of pores, and wall thickness vary from one method to another. To tune these parameters for intended application, morphological characterization is essential. Morphological characterization reveals the shape, size, porosity, and size distribution of pores of the hydrogel which must be known to control or tailor these parameters for the desired application [97].

Morphological analysis of hydrogels is quite difficult due to the delicate nature of the system and chance of collapse of pore structure during dehydration. However a number of techniques are available for microstructural analysis of hydrogels like

scanning electron microscopy (SEM), laser scanning confocal microscopy (LSCM), confocal laser scanning fluorescence microscope (CLSM), fluorescence microscope (FM), etc., but the contrast and resolution of the microscope system are very important; lack of which can lead to poor images [98].

3.1 Scanning Electron Microscopy of Chitosan-Based Hydrogels

For morphological characterization of hydrogels by SEM, special sample preparations are required. To observe the surface morphology, after gelation, hydrogel samples are quickly frozen in refrigerator or in liquid nitrogen and further lyophilized with a freeze dryer system under vacuum at −50 °C to −70 °C for at least 48 h until all of the water is sublimed [99]. The sample is then mounted on a metal stub usually made of aluminum with conductive tape and is coated with metal for conductance under vacuum by a sputter. Gold is used to coat the freeze-dried sample widely, but gold-palladium or platinum are also used [96, 100]. To observe the interior morphology, i.e., cross-sectional view of hydrogels, the freeze-dried hydrogels are usually fractured and then sputter-coated with metal [99].

When chitosan is chemically cross-linked to prepare hydrogel, the degree of cross-linking can affect the bulk and surface morphology of freeze-dried hydrogels. In case of hydrogel of chitosan prepared by chemically cross-linking with glutaraldehyde, the concentration of glutaraldehyde governs the size and distribution of pores. Increase in concentration of glutaraldehyde causes the growth of pore size and decreases their distribution by restricting the free movement of the polymer chains. As a result, the swelling ratio of the prepared hydrogel also decreases. As the pore size of hydrogel can significantly change gel swelling, it can also affect the properties of hydrogel like drug delivery behavior, enzyme activity, biocompatibility, etc., hence the importance of morphological analysis [101].

Polyacrylamide-chitosan hydrogel, a chitosan-based hydrogel, was found to have the ability to release drug in a sustained manner [96]. The surface and cross-sectional morphology of the freeze-dried hydrogel was examined by SEM which revealed porous nature of the matrix with interconnected channel-like structures. The SEM images also helped to compare the nature of polyacrylamide-chitosan hydrogel over pure chitosan matrices which are fragile and exhibit uncontrollable porosity. The freeze-dried hydrogel showed a faster and extensive swelling which can be explained by the morphological analysis. As the hydrogel has interconnected pores, these channel-like structures can take up the water phase in the matrix by capillary action, and as a result swelling is achieved by fast diffusion of solvent in the matrix. Thus morphological characterization helps to explain various physical properties of hydrogel like hydrophilic nature, hardness, swelling behavior, etc.

In case of gelatin/carboxymethyl-chitosan hybrid hydrogel prepared by radiation-induced-cross-linking intended to be used in tissue engineering where porous microstructure plays significant influence, SEM images can confirm the nature and interconnected structure of the pores (Fig. 11). By measuring the pore diameter in SEM images, it is also possible to observe the effect of variation in the ratio of

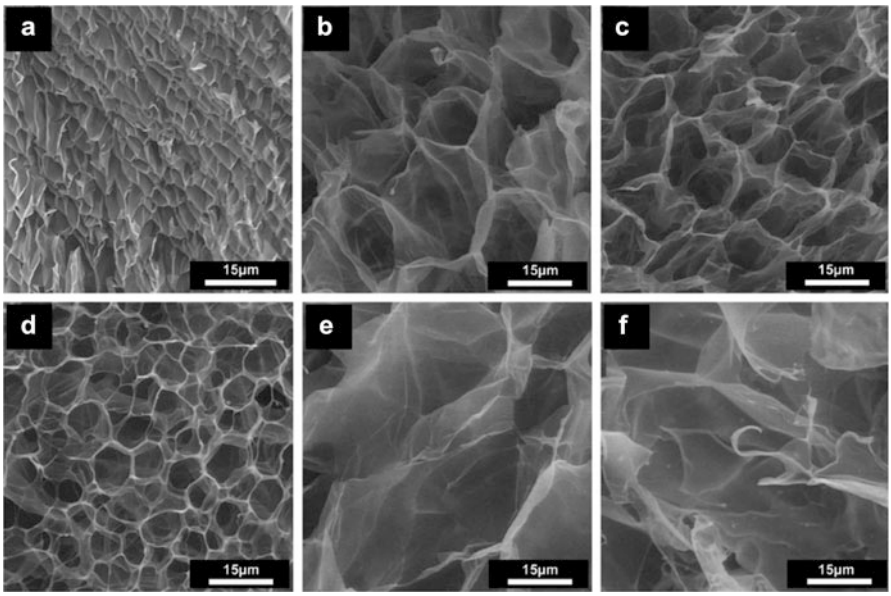

Fig. 11 The scanning electron micrographs of the lyophilized gelatin/carboxymethyl-chitosan hydrogels prepared at different ratios of gelatin to carboxymethyl-chitosan. Open and interconnected porous structures are clearly visible in each image. (Reprinted with permission from [102] Copyright © 2010, Elsevier)

gelatin/carboxymethyl-chitosan on pore sizes and the thickness of the wall of prepared hydrogel scaffolds [102].

SEM images also help to explain the effect of pH of the solution on the structure of hydrogel. In a hydrogel system composed of *N*-[(2-hydroxy-3-trimethylammonium) propyl] chitosan chloride (HTCC) and glycerophosphate (GP), it was found that the structure of the hydrogel changed greatly after dipping in acidic and basic solution [100]. The original HTCC/GP hydrogels had more compact structure due to low crystallinity and high uniformity of HTCC, but after dipping in acidic solution, large pores were observed in the network (Fig. 12a). The reason behind formation of these pores was good hydrophilicity of HTCC, i.e., the cationic quaternized chitosan dissolved quickly in acidic solution. As chitosan is insoluble in basic medium, the structure HTCC/GP hydrogel did not change apparently when dipped in basic solution (Fig. 12b).

The effect of constituent's molecular weight on the structure of hydrogel can also be determined by analyzing SEM images. An injectable triple cross-linking network hydrogel prepared from chitosan and poly(ethylene glycol) diacrylate (PEGDA) was found to have a highly macroporous, sponge-like structure with average pore size of 20–60 μm [99]. However, changing the molecular weight of one of the constituents PEGDA, it was found that the pore size became larger with the increase of molecular weight of PEGDA. This phenomenon arises because PEGDA with higher molecular

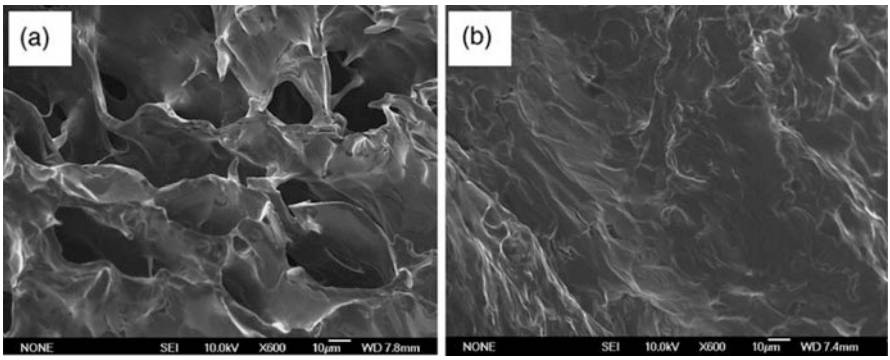

Fig. 12 SEM micrographs of HTCC/GP hydrogel after immersion in buffer (**a**) at pH 5.0; (**b**) at pH 7.4. (Reprinted with permission from [100] Copyright © 2006, Elsevier)

weight has better solubility and helps it to stretch sufficiently to create a larger pore size network. Such porous structure of hydrogel is helpful for the delivery of macromolecular compounds as they can diffuse freely into the pores.

In nanocomposite hydrogels like chitosan-iron oxide coated graphene oxide (GIO) nanocomposite hydrogel prepared by gel casting technique, SEM images help to observe the nature of distribution of nanomaterials in the polymeric hydrogel matrix. From SEM images, the chitosan-GIO nanocomposite hydrogel was found to have a compact packing of hydrogel network macrostructures with surface roughness which is the unique morphology of hydrogel prepared by gel casting technique. It is also possible to tune the surface properties like hydrophobicity which can be changed by varying the loading percentage of iron oxide coated graphene oxide nanomaterial in the chitosan matrix by analyzing SEM images [103].

Silver nanoparticles loaded poly(vinyl alcohol)/chitosan hydrogel thin films is another chitosan-based nanocomposite hydrogel prepared via ultraviolet (UV) irradiation [104]. The surface and cross-sectional morphologies of the PVA/chitosan hydrogel (PCA) and the Ag nanoparticles loaded composite (PCA/Ag) were revealed in SEM images. Interconnecting pore structures were observed in the top surface of the PCA thin film with the pore size in the submicron scale (Fig. 13a), but in case of PCA/Ag composite, expanded pore structures were observed with uniform distribution Ag nanoparticles in the composite (Fig. 13b and c).

3.2 Laser Scanning Confocal Microscopy of Chitosan-Based Hydrogels

Although SEM is the most established method to observe the morphology of hydrogel because of its ability to provide structural information in sufficient detail, this technique suffers from some disadvantages of which collapse of pore structure

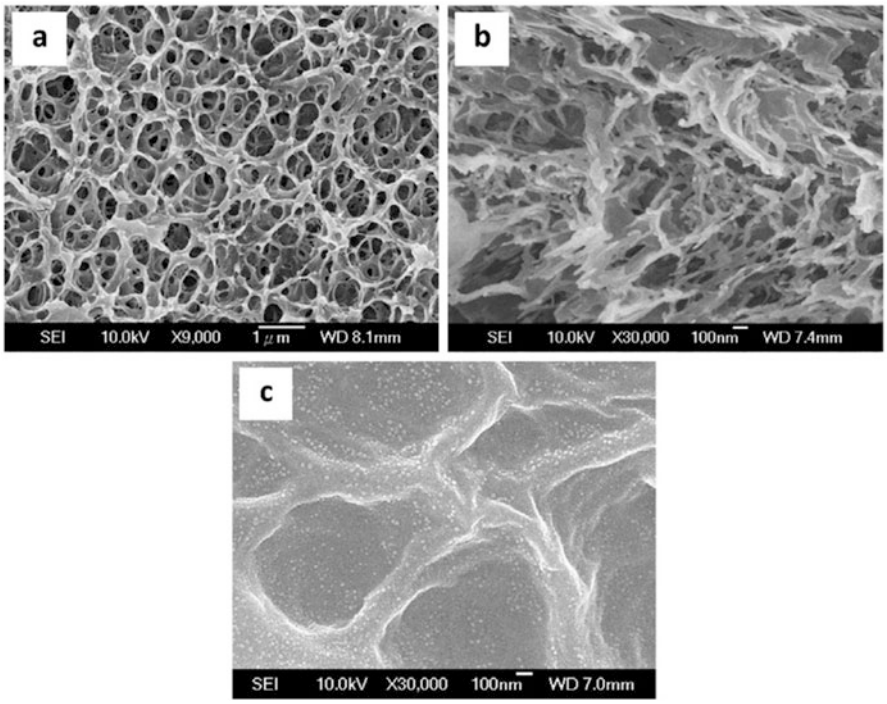

Fig. 13 SEM images of the cross section of (**a**) PCA, (**b**) and (**c**) PCA/Ag. (Reprinted with permission from [104] Copyright © 2014, Elsevier)

during dehydration leading to volume shrinkage is the most serious one. In the native state, hydrogel contains substantial amount of water which must be removed prior to SEM examination that affects the morphology of hydrogel.

Two common methods used to dehydrate hydrogels prior to examination by SEM are freeze-drying and critical point drying [105]. In case of freeze-drying, if the rate of freezing is too slow, then ice crystals are formed instead of vitreous ice which can cause damage to the sample. In case of critical point drying, the hydrogel may melt if the temperature required to reach supercritical conditions is above the glass transition point of the hydrogel resulting in distortion or destruction of pore structure. Moreover to examine the internal structure, freeze-dried hydrogel has to be fractured which causes further impairments.

Laser scanning confocal microscopy (LSCM) is an alternative method to investigate the morphology of hydrogel in its native state, i.e., hydrated state. It is a far simpler and more rapid technique for imaging hydrogels than SEM. LSCM allows to take images of hydrogel without fracturing or cutting the sample [106]. In this method a series of images taken at successive intervals and by magnifying special region of interest can be superimposed to get detailed morphological information. With the help of application software that utilizes a series of successive LSCM images, the three-dimensional nature of hydrogel can also be observed.

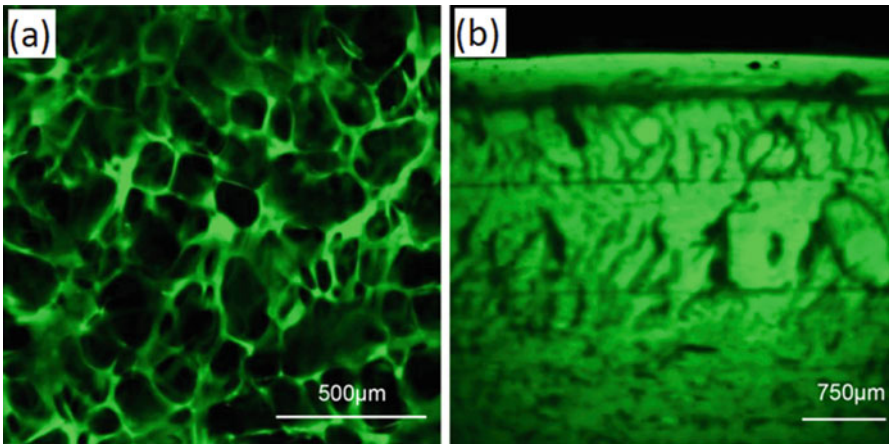

Fig. 14 Morphology of chitosan hydrogel prepared by single-opening mold (**a**) LSCM image, concentration of chitosan is 0.1 wt.%, cross section (**b**) LSCM images, concentration of chitosan is 4.0 wt.%, longitudinal section [98]

The basic principle of LSCM includes labeling the hydrogel sample with a fluorescent dye and excitation of the sample by laser light. The emitted red-shifted light from the fluorescent dye is then detected and used to construct an image. As both labeling and imaging can be carried out in the hydrated state of hydrogel so no dehydration of hydrogel is required, as a result the aforementioned problems encountered in SEM can be avoided [105].

Typical sample preparation for LSCM involves soaking of hydrogel sample in aqueous solution of fluorescent dye, e.g., fluorescein isothiocyanate or rhodamine B isothiocyanate for about 24 h. To remove excess dye, the sample is rinsed off with distilled water for several times. The rinsing operation is carried out in the dark to prevent photobleaching of the dye, and after completion of washing, the sample is usually stored in dark at 4 °C [105].

Morphological analysis plays a vital role in design and fabrication of multilayered chitosan hydrogel with oriented structure. Multilayered chitosan hydrogel was prepared by gelation process without any auxiliary cross-linking agent [98]. The effect of concentration of chitosan on hydrogel was observed and found that orientation of layers in hydrogel cannot always be observed. When chitosan concentration was less than 0.5 wt.%, an ordinary random porous 3D network was formed without formation of any layer (Fig. 14a). But when the concentration was higher than 1.0 wt.%, oriented multilayered structure with spatially separated layers was observed (Fig. 14b). As the orientation only observed in hydrogels with relatively high concentration of chitosan, so polymer concentration played an important role in the formation of hydrogel. Again the method of preparation has effects on formation of layers in hydrogel. In LSCM images, the layers are clearer when the hydrogels are prepared by cylindrical mold than single-opening mold. Hydrogel prepared by cylindrical mold showed layers were formed in the form of concentric circles and orientation presented a radial pattern

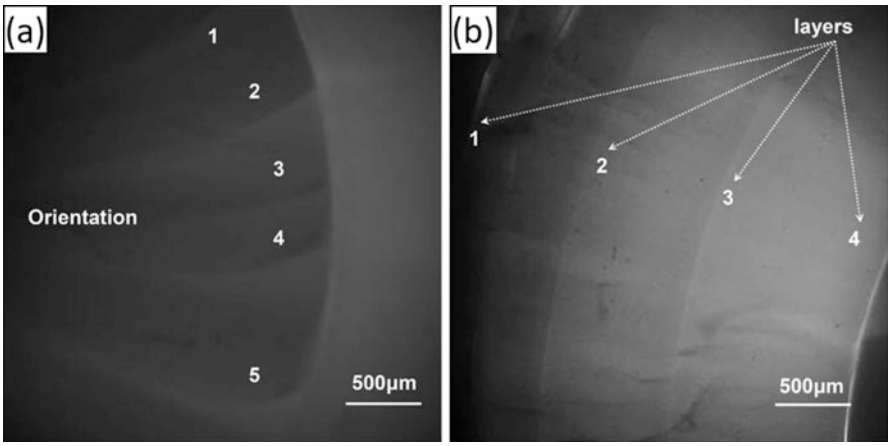

Fig. 15 Morphology of chitosan hydrogel prepared by cylindrical mold (**a**) Orientation in radial pattern, LSCM image, bright field; (**b**) concentric layers, LSCM image, bright field [98]

(Fig. 15a and b). It is important to understand such layered-oriented structure and direction of orientation through morphological analysis to control and design the structure of hydrogels.

In case of chitosan/glycerophosphate (GP) hydrogel, a chitosan-based thermosensitive hydrogel, LSCM has found to be a valuable technique for imaging hydrogel microstructure which provides both qualitative and quantitative data as well as helps to understand the gelation mechanism [97]. A comparative study of morphology of this hydrogel by analyzing images of two techniques, SEM and LSCM, was also carried out. From LSCM images it was found that chitosan/GP hydrogel had a heterogenous, beaded, open network structure formed by linking polymeric aggregates in agglomerates and chains, while SEM images failed to detect this fine aggregate structure. The effect of variation of chitosan content in hydrogel was also observed, and it was found from confocal images that the polymer-rich phase increased with increasing chitosan content (Fig. 16).

One of the unique features of LSCM analysis is the visualization of three-dimensional structure of hydrogel. Utilizing a series of successive LSCM images of chitosan/GP hydrogel, the three-dimensional nature of hydrogel was observed which ensured random microstructure in all dimensions (Fig. 17).

4 Morphological Characterization of Collagen-Based Hydrogels

Collagen is the most abundant protein in mammals and the main structural component in the connective tissue of extracellular space. Degree of mineralization decides whether collagen tissue would be rigid (bone) or compliant (tendon). Cartilage is a special kind of collagen tissue which inclines from hardness to flexibility.

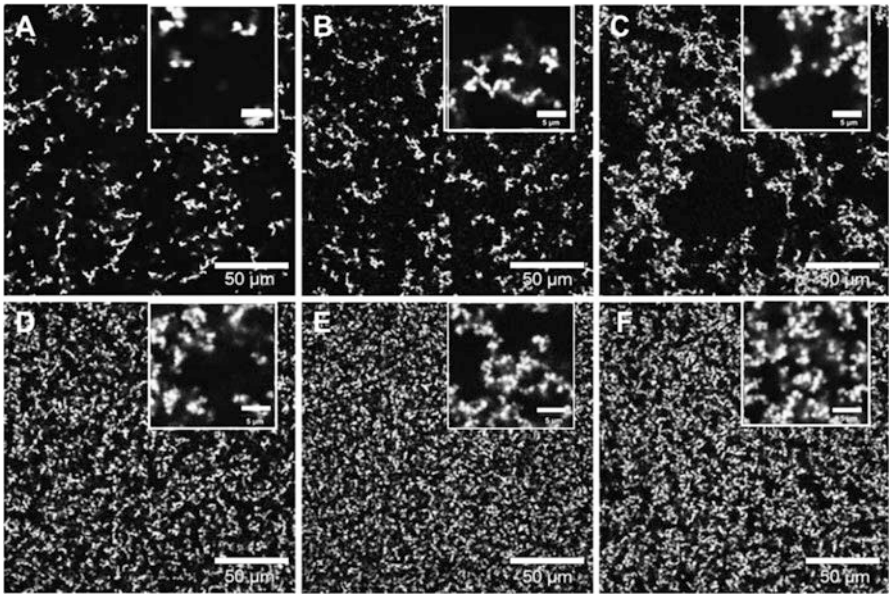

Fig. 16 LSCM images of chitosan/GP hydrogel with variations in chitosan content. Inset optically magnified 10X. Chitosan compositions: (**a**) 0.25 wt.%/vol.%, (**b**) 0. 5 wt.%/vol.%, (**c**) 0.75 wt.%/vol.%, (**d**) 1.0 wt.%/vol.%, (**e**) 1.25 wt.%/vol.%, (**f**) 1.5 wt.%/vol.%. White areas represent the polymer-rich phase. (Reprinted with permission from [97] Copyright © 2005, Elsevier)

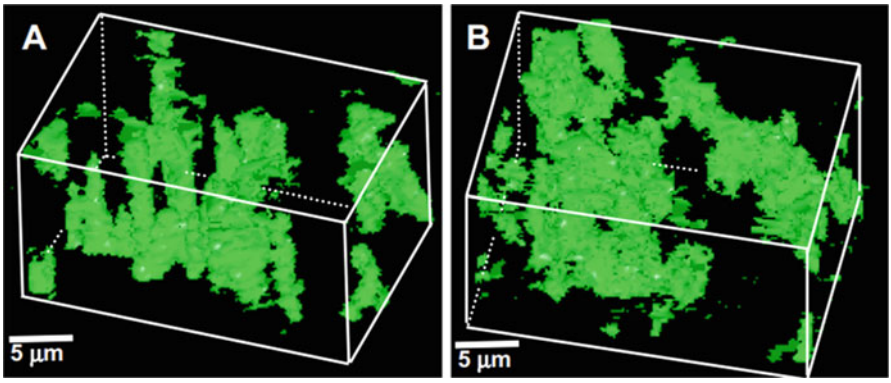

Fig. 17 Three-dimensional visualizations of chitosan/GP gels, using stacked LSCM images. (**a**) 0.25 wt.%/vol.% chitosan, (**b**) 1.0 wt.%/vol.% chitosan. (Reprinted with permission from [97] Copyright © 2005, Elsevier)

According to Robert H. Bogue, collagen is not a simple anhydrous of gelatin but rather a polarized complex produced by chemical condensation [107]. Collagen becoming a natural product has extensive use in wound healing [108], bone grafting [109], and regeneration of tissue by scaffolding [110].

The water sorption ability and swelling kinetics of a hydrogel depend on the porosity of hydrogels. For instance, to make available space for cell seeding, growth, and proliferation, optimum porosity of hydrogel for tissue regeneration is ranging from 5 μm in neovascularization to 100–350 μm in bone regeneration [111]. Therefore, increment of porosity in hydrogels is regarded as the most important issue in most researchers. It can be achieved in collagen-based hydrogels either by physical or chemical techniques. The chemical techniques may encompass phase-separation, foaming, lyophilization, solvent casting, particulate-leaching, etc. [28], while the physical techniques may include laser sintering [29] and laser -enhanced surface modification [30].

4.1 Scanning Electron Microscopy of Collagen-Based Hydrogels

It is mentioned earlier in this chapter that extensive sample preparations are required for the capturing the SEM images of an object to monitor the surface morphology. A. Pourjavadi et al. observed the porosity of a collagen-based hydrogel which was prepared by chemically modifying collagen with acrylamide (AAm), acrylic acid (AA) [AAm:AA = 2.17], and *N, N* –methylene bis acryl amide (MBA), where grafting was initiated by potassium polysulfate (KSP) and subsequently neutralized by sodium hydroxide [112]. They depicted SEM images in Fig. 18 which showed

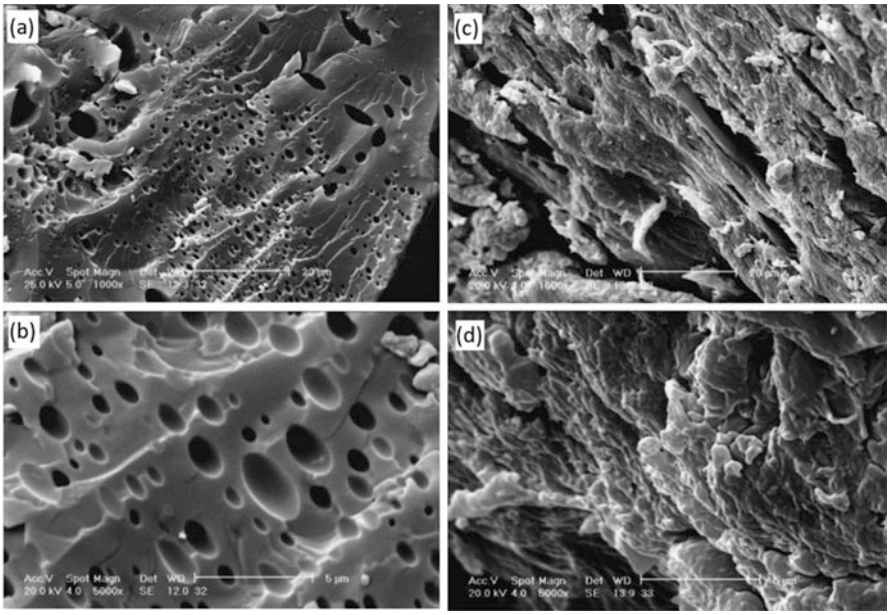

Fig. 18 SEM photographs of the optimized superabsorbent hydrogel (collagen 1.33 g, AAm/AA 2.17, MBA 5.6 mmol/l, KPS 2.1 mmol/l) neutralized after gel formation (**a**) 1000×, (**b**) 5000× and neutralized before gel formation (**c**) 1000×, (**d**) 5000×. (Reprinted with permission from [112]. Copyright © 2007, Elsevier)

that the porous structure was more prominent in grafted copolymers due to neutralization after the gel formation. They assume water evaporation resulting from the neutralization heat introduced more in the hydrogels.

Clay-free composite hydrogels usually show higher porosity than its counterparts. It appeared in an investigation of Kabiri et al. that porogen has lost its efficiency in presence of clay while producing porous collagen-based composite incorporating poly (AA-co-potassium acrylate) and kaolin in collagen matrix [113]. They investigated the morphology of superadsobent hydrogel composite with different porogens such acetone, sodium bicarbonate, and acetone-sodium bicarbonate in combined. It was observed that porosity was lowered considerably due to addition of kaolin [113].

The type of clay is also an important factor that influences the porosity of superadsobent composite. Zhang et al. examined the impact of five different clays including attapulgite, kaolinite, mica, vermiculite, and montmorillonite on absorption rate of a superabsorbent hydrogel composite [114]. It was found montmorillonite-composite displayed the highest swelling capability probably due to its higher porosity in the matrix [114]. Nistor et al. investigated the porosity of superabsorbent hydrogel composite intercalating three types of montmorillonite nanoclays – Dellite® HPS (HPS), Dellite® G67 (G), and Cloisite® 93A (C). Dellite® HPS nanoparticles are natural nanoclays, respectively, a purified montmorillonite unmodified, while Dellite® 67G is a nanoclay deriving from a naturally occurring montmorillonite especially purified and modified with a high content of quaternary ammonium salt (dimethyl dihydrogenated tallow ammonium). Cloisite® 93A nanoparticles are products of Southern Clay Products which are natural montmorillonites modified with a ternary ammonium salt, respectively, methyl dehydrogenated tallow ammonium, for an organic modifier concentration of 95 meq/100 g clay [115]. The SEM images showed in Fig. 19 displays the evidence of disorganized porous structures of the all types of hydrogels, where hybrid hydrogel impregnated with Dellite® HPS showed the largest size of pores of 60 ± 5 μm and hybrid hydrogel impregnated with Dellite® G67 showed the smallest size of pores of 30 ± 10 μm. From their experiments, Nistor and his coworkers emphasized that the uniform distribution of pores depended on the electrical charge of the nanoclays and types of the ions in the chemical structure of the hydrogel matrix [115].

4.2 Atomic Force Microscopy of Collagen-Based Hydrogels

Atomic force microscopy (AFM) is a powerful tool for surface analysis. To know the surface topography with nano or even atomic resolution AFM has been contributing widely since early 1980 [116]. While the electron microscope provides a two-dimensional projection or image of a sample, the AFM delivers three-dimensional surface details. In addition, AFM does not require any extensive sample preparation (such as carbon or metal coatings) which is mandatory for SEM or TEM. Above all, high-resolution AFM conveys comparable information in consideration with SEM, TEM, and STM.

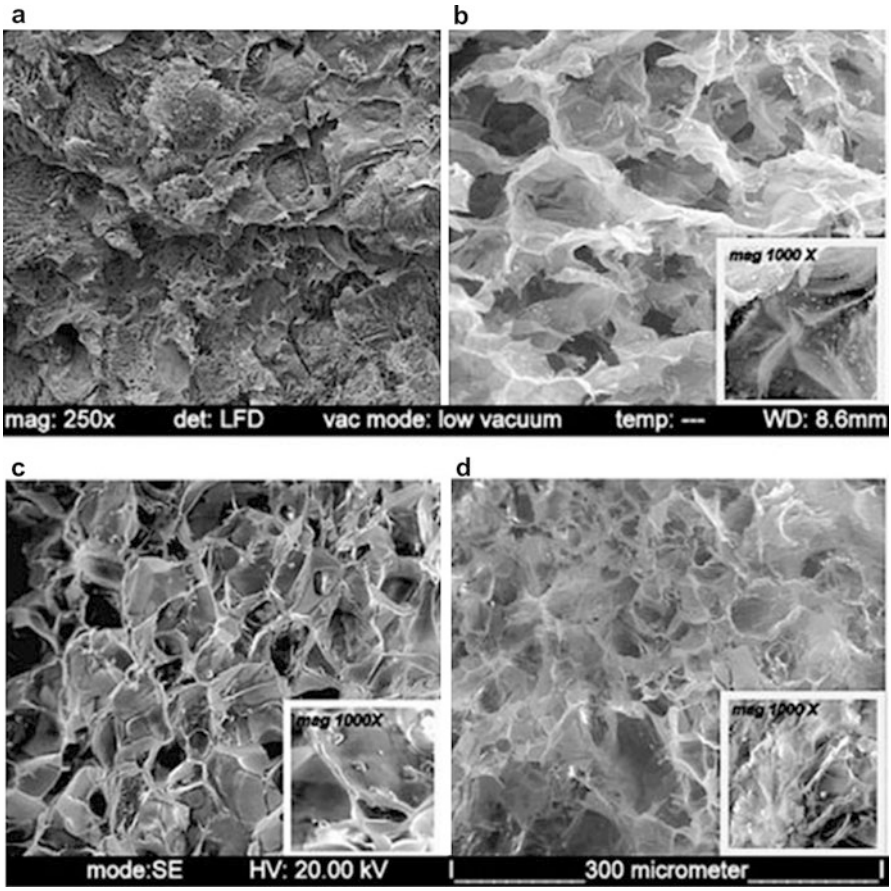

Fig. 19 SEM images of (**a**) hydrogel without montmorillonite, (**b**) hybrid hydrogel intercalated by Dellite® HPS, (**c**) hybrid hydrogel intercalated by Dellite® G67 and (**d**) hybrid hydrogel intercalated by Cloisite® 93A. (Reprinted with permission from [115] Copyright © 2015, Elsevier)

In the field of tissue engineering, such as skin burns, wound healing, etc., roughness of the surface plays an important role. For healing of burned tissue, slightly rough surface in the hydrogels is generally desired [117]. As mentioned earlier in the immediate previous section of SEM of superabsorbent hydrogel intercalating montmorillonite nanoclays, Nistor and his coworkers also observed the surface roughness through AFM [115]. In Fig. 20, comparatively even surface was exhibited in case of hydrogel without montmorillonite nanoparticles, while a nodular morphology and extended structure were observed on the surface of hybrid hydrogels. Due to incorporation of Cloisite® 93A, Dellite® HPS, and Dellite® 67G, the average roughness of the hybrid hydrogels increased to 8.14 ± 0.63 nm, 15.64 ± 1.05 nm, and 17.32 ± 0.87 nm, respectively, where surface of the hydrogel without nanoclays found considerably smooth

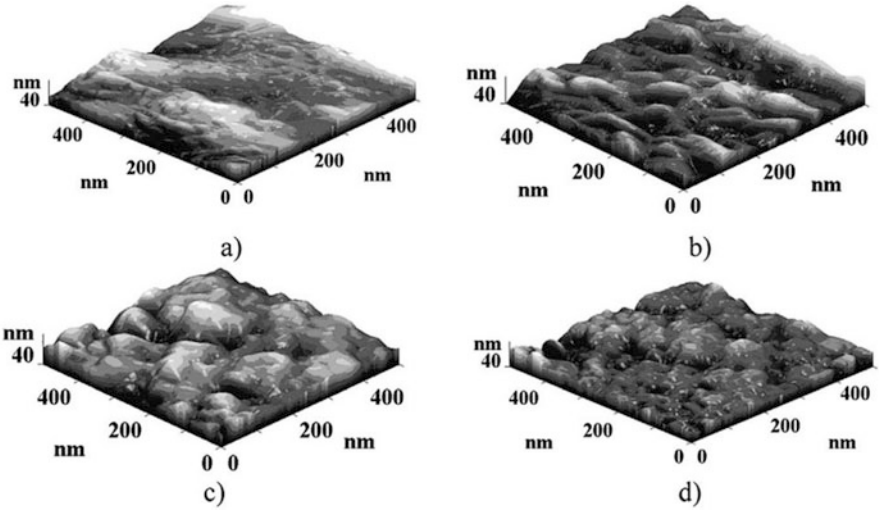

Fig. 20 AFM images (500 × 500 nm) of (**a**) polymeric hydrogel without nanoclay and hybrid hydrogels with (**b**) Dellite® HPS, (**c**) Dellite® 67G, and (**d**) Cloisite® 93A. (Reprinted with permission from [115] Copyright © 2015, Elsevier)

(4.27 ± 0.08 nm). It appeared that the surface morphology depends on nanoparticle type. The selective accession of crowded montmorillonite nanoparticles to the polymer chain (attachment of nanoparticles to the functional groups of polymers) during the synthesis of hybrid hydrogels influenced the roughness texture and uniformity of surface.

5 Morphological Characterization of Gelatin-Based Hydrogels

Gelatin is an assortment of peptide and proteins produced by partial hydrolysis of collagen extracted (by chemical denaturation) from the skin, bones, and connective tissues of animals such as domesticated chicken, cattle, pigs, and fish [118]. During hydrolysis, the natural molecular bonds between individual collagen strands are broken down into a form that rearranges more easily. Its chemical composition is, in many aspects, closely similar to that of its parent collagen [119]. Gelatin is generally consist of carbon, 6.8% hydrogen, 17% nitrogen, and 25.2% oxygen [120]. Gelatin has extensive use in food, pharmaceutical, cosmetic, and photographic industries, as it has the distinctive functional properties. In the field of food industry, gelatin is regularly being used in bakery, dairy, beverages, and confectionary for gelling, emulsification, texturization, and stabilization [121]. In the meantime, gelatin is widely being used in drugs encapsulation (both as hard and

soft form), ointment filling, wound dressing, plasma expanding, and emulsification in pharmaceutical industries [122]. Moreover, gelatin has been applied as emulsion layer, non-cult layer, and coating layer on the photographic materials [123].

5.1 Scanning Electron Microscopy of Gelatin-Based Hydrogels

As mentioned previously in this chapter, hydrogels can be prepared either using chemical method [28] or physical method [29]. Interconnection of pores cannot be assured in the hydrogels which are generally produced by chemical methods, even the organization of pore size are complicated due to uneven evaporation during drying. Moreover, risk of toxicity and carcinogenicity due to existence of residual solvent discourages hydrogels produced by chemical method for application of public health [124].

In concern with physical well-being, physical approaches of hydrogel preparation are more attractive in opposition to chemical techniques. Physical method like femtosecond laser for modification is a one-step process with precision, noncontiguous to chemicals or solvents, and free from objectionable thermal damage [126]. Daskalova et al. displayed the efficacy of application of femtosecond laser pulses for successful modification of surfaces of gelatin thin films, for creation of micro- and nanoscale structures [125]. Laser used by them was a CPA Ti: sapphire laser (Femtopower Compact pro) emitting at 800 nm central wavelength, with pulse duration of 25 fs, at repetition rate of 1 KHz, and average output power of 800 mW. Condition used for the treatment was air and sample object was placed few mm away to avoid nonlinear optical effect of air. The size of the spot was 182 μm measured by shot diameter regression technique [127]. The films of gelatin were irradiated with various fluences (a stream of particles crossing a unit area, generally represented by F with a unit of Joule per square cm) and various numbers of pulses (unitless and dimensionless parameter generally represented by N). Then the irradiated thin films of gelatin was observed utilizing SEM [125].

Daskalova et al. noticed the formation of the rim surrounding the central area of the spot ($N = 1$) in Fig. 21a and another new rim formation in Fig. 21b due irradiation of second pulse ($N = 2$). The effect of rim formation was reproducible even when lager number of pulses was applied on the films exhibited in Fig. 21c–f. The formation of rim is considered as a consequence of the splash of a resolidified molten material generated during the process of laser impact. Due to larger impact of the laser, the formation of a crater in the center started to form at 25 pulses ($N = 25$) and a hole was witnessed at 100 pulses ($N = 100$). Higher degree of magnification of SEM images were showed in Fig. 22a–d where it was observed that porosity of the matrix started to generate (Fig. 22b) at lower pulse (N = 2) and became obstructed (Fig. 22d) at higher pulses (N = 25). This alteration was explained as melting-freezing or sublimation-deposition of gelatin in the inner irradiated area. This phenomenon assured the researchers to adjust the structure of the gelatin film for their special purposes [125].

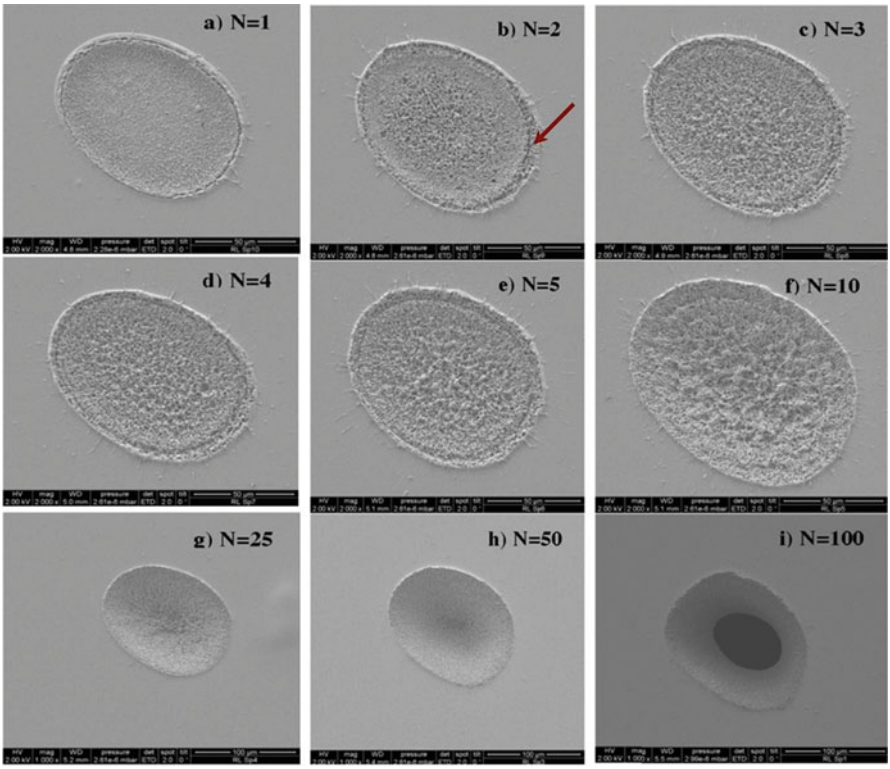

Fig. 21 SEM images (2000×) of a surface modification of thin gelatin film irradiated at λ= 800 nm, T= 30 fs laser pulse and laser fluence F = 2.5 J/cm2: (**a**) $N = 1$, (**b**) $N = 2$, (**c**) $N = 3$, (**d**) $N = 4$, (**e**) $N = 5$, (**f**) $N = 10$, (**g**) $N = 25$, (**h**) $N = 50$, (**i**) $N = 100$. (Reprinted with permission from [125] Copyright © 2013, Elsevier)

6 Morphological Characteristics of Synthetic Polymer Hydrogels

Hydrogels are the three-dimensional polymer networks that are swollen by trapping large amounts of water. Those networks are formed by molecular self-assembly through covalent, ionic, or hydrogen bonds [128]. According to the sources, hydrogel can be classified into those formed from synthetic polymers and those formed from natural polymers. Both types of hydrogels have versatile applications in food products to medical purposes. Owing to the adjustable mechanical properties, ability for photopolymerization, and easy control of scaffold architecture and chemical compositions, the demand of synthetic polymer hydrogel has increased exponentially [129]. Among the vast polymer application, only limited polymers have the ability to form hydrogel networks. Some of the synthetic polymer-based hydrogels have been reported such as poly(ethylene glycol) [37], poly(vinyl alcohol) [33], poly

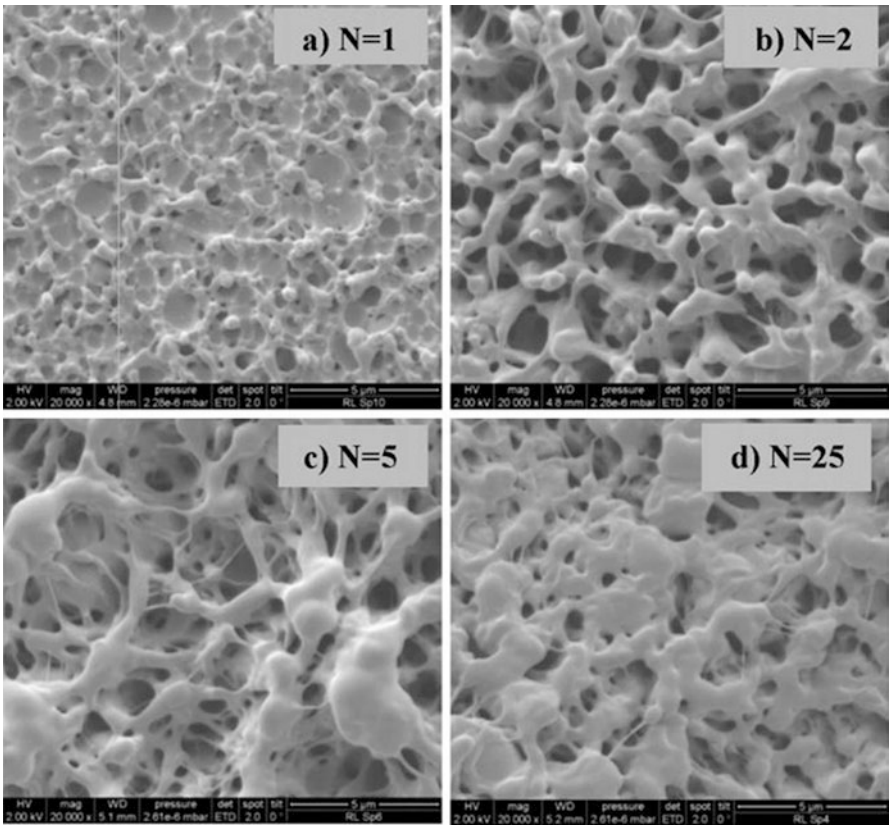

Fig. 22 Higher SEM resolution images (20,000×) of a surface modification of thin gelatin film irradiated at λ= 800 nm, T= 30 fs laser pulse and laser fluence F = 2.5 J/cm^2: (**a**) $N = 1$, (**b**) $N = 2$, (**c**) $N = 5$, (**d**) $N = 25$. (Reprinted with permission from [125] Copyright © 2013, Elsevier)

(amido-amine) [36], poly(*N*-isopropylacrylamide) [34], polyacrylamide [38], and poly(acrylic acid) [35] and their copolymers [130]. The physical characteristics such as amount of void space, pore size, wall thickness, etc. vary from polymer to polymer, fillers as well as preparation method. In general, the pore size increases with an increasing swelling ratio of the hydrogels [131]. The sampling for morphology analysis of synthetic polymer was similar to natural polymers.

Polyaniline-polyvinyl alcohol (PANI-PVA) hydrogel, a PVA-based hydrogel, was reported as self-supported electrode for supercapacitors [132]. The aniline monomer was dissolved in acidic PVA solution and performed in situ polymerization, accompanied with freezing-thawing gelation of PVA. The morphology of this composite hydrogel was observed by Field Emission Scanning Electron Microscopy (FESEM), and the FE-SEM images of PVA and PANI-PVA hydrogel are presented in Fig. 23. It is revealed that pure freeze-dried PVA hydrogel shows nanoporous morphology with pore size ranging from several micrometers to nanometers (Fig. 23a). In contrary,

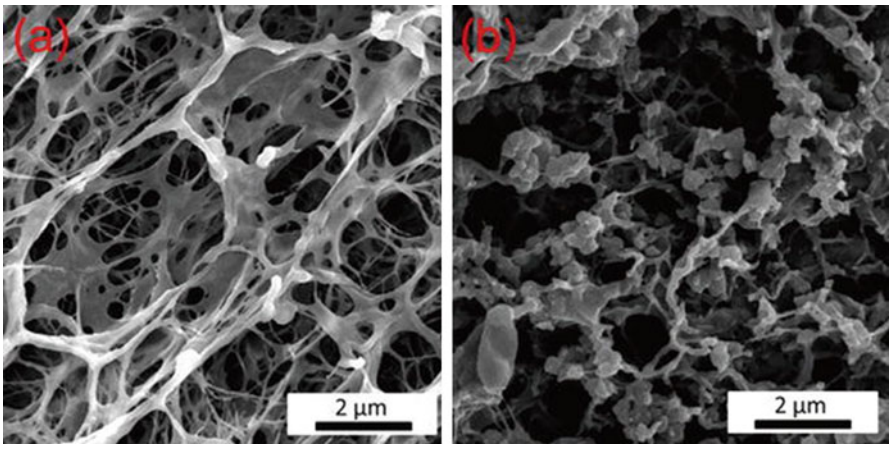

Fig. 23 FE-SEM images of (**a**) PVA and (**b**) PANI-PVA hydrogel. (Reprinted with permission from [132] Copyright © 2016, Springer Science+Business Media New York)

incorporated PANI/PVA hydrogel maintains the nanoporous PVA chain structure with some nanoaggregates of nanorods, nanosheets, and nanoparticles formed from PANI chains (Fig. 23b). The uniformly distributed PANI nanoaggregates can provide ion/electron transmission channel for electrochemical reactions within the PANI/PVA hydrogel and enhances the suitability as a supercapacitors.

Xu et al. have prepared controlled porous structure PVA-based hydrogels by freezing technique. The influence of poly(ethylene glycol) (PEG) on the microstructure was investigated by SEM and found that the porosity of hydrogels was significantly increased with PEG incorporated and the pore size increased with the increasing of PEG molecular weight [133]. Shi et al. have reported contrary results in PVP-PVA composite hydrogel. The results showed that with the increasing polymerization degree and polymer concentration of PVA, the network structure of hydrogels became denser and porosity significantly decreased [134]. Shi et al. have also synthesized and characterized PVP/PVA hydrogel for the applications of articular cartilage replacements [135]. The SEM images of PVA/PVP hydrogels before and after swelling in non-osmotic and osmotic solutions for 28 days are presented in Fig. 24. The SEM images revealed that all hydrogel samples showed three-dimensional porous network structures. But after immersing the hydrogel in osmotic solution, the microstructure became dense due to hydrogel deswelling in osmotic solution.

Bhowmick and Koul synthesized silver nanoparticles (AgNPs) loaded antimicrobial hydrogel PVA dressing scaffold by using freeze-thaw method [136]. The morphology of PVA hydrogel and AgNPs loaded PVA hydrogels had been characterized by scanning electron microscopy (SEM) at 5000 magnification. The SEM micrograph of both hydrogel shows a microporous web-like structure (Fig. 25). No segregation of AgNPs in hydrogel was observed and indicated strong interaction between Ag and polymers.

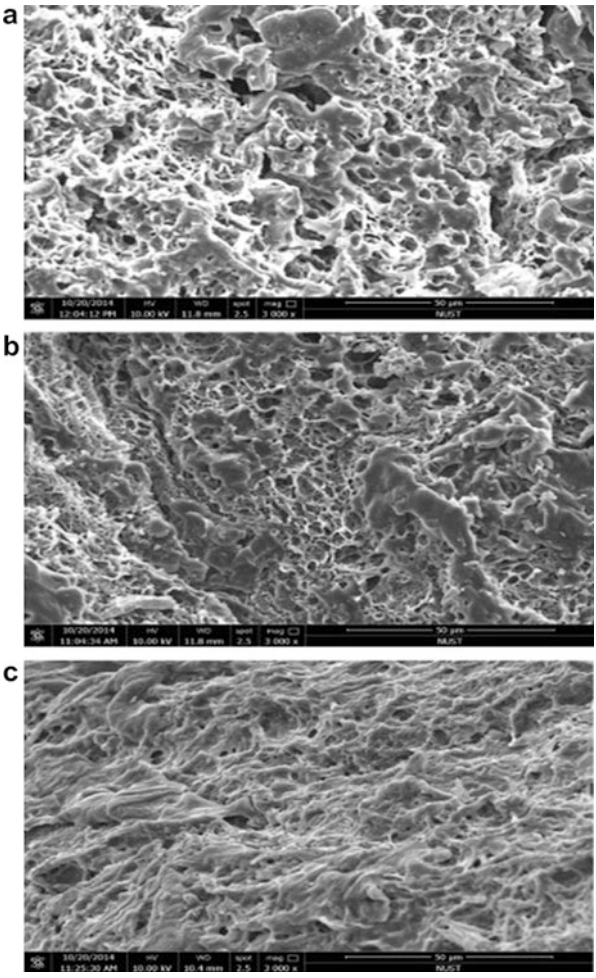

Fig. 24 SEM micrographs of the (**a**) PVP/PVA hydrogel, (**b**) after swelling in non-osmotic solution PVP/PVA hydrogel, and (**c**) after swelling in osmotic solution PVP/PVA hydrogel. (Reprinted with permission from [135] Copyright © 2016, Elsevier)

Yu et al. prepared silver nanoparticles incorporated poly(vinyl alcohol)/poly(*N*-vinyl pyrrolidone) (PVA-PVP) hydrogels by repeated freezing-thawing treatment [137]. The surface and cross-sectional morphologies of Ag/PVA-PVP composite hydrogels were investigated by SEM; both PVA-PVP and Ag/PVA-PVP hydrogels showed porous dimensional network structure. No distinguished difference was found among the hydrogels with different silver contents due to stable network structure within hydrogel and the strong interaction between the silver particles and the PVA and PVP molecules. Owing to excellent antibacterial ability, superb water retention ability and good oxygen transportation capability, Ag/PVA-PVP may be used a potential wound care dressing.

Hu et al. have prepared polyvinyl alcohol/carbon dot (PVA/C-dot) hydrogel by freeze-thaw method, and Ag nanoparticles was simply introduced to enhance the

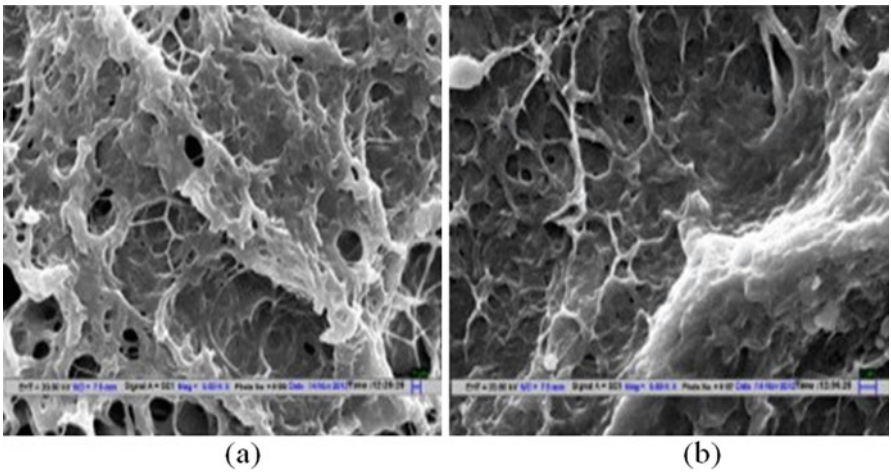

Fig. 25 SEM images of (**a**) PVA hydrogel and (**b**) AgNPs loaded PVA hydrogel (at 5000 magnification). (Reprinted with permission from [136] Copyright © 2015 Elsevier)

antimicrobial activity and enlarge their application potential in medical field [138]. The morphology of this composite hydrogel was investigated by SEM and observed that nanoparticles were uniformly dispersed in PVA/C-dot-Ag hydrogel. The mapping image also showed that the Ag element was uniformly dispersed in PVA/C-dot-Ag hydrogel, indicating uniform dispersion of Ag nanoparticles in PVA/C-dot-Ag hydrogel.

Chen et al. have reported contrary morphology of graphene oxide (GO)-reinforced PVA hydrogels with compared other inorganic nano fillers PVA hydrogel [139]. They synthesized inorganic/organic interpenetrating network (IPN) hydrogels using a freeze-thaw method with a modified GO which was cross-linked by β-cyclodextrin aldehyde (β-CD-DA) to form an inorganic GO network (β-GO). The structure of the hydrogels was investigated by scanning electron microscopy, and the SEM images of PVA hydrogel, β-GO (1, 2, and 3 mg/ml)/PVA hydrogel and pristine GO (1, 2, and 3 mg/ml)/PVA hydrogels are shown in Fig. 26. In the SEM micrograph, PVA hydrogel shows porous structures. The other hydrogels displayed dense structures regardless of whether GO or β-GO was present. The incorporation of GO can efficiently fill pores in pure PVA hydrogels.

Poly(*N*-isopropylacrylamide) (PNIPAAm)/poly(vinyl alcohol) (PVA), a PVA-based temperature-sensitive semi-interpenetrating polymeric network (IPN) hydrogel, was found to have the fastest temperature responsive properties [140].The PNIPAAm networks were cross-linked by *N*,*N*′-methylenebisacrylamide (MBAAm) in the presence of linear PVA. The prepared semi-IPN hydrogels were characterized for their morphologies by scanning electron microscopy, and the SEM micrograph of the freeze-dried hydrogels is shown in Fig. 27. It was found that the hydrogel morphologies were dependent on the feed compositions of PNIPAAm and PVA. The morphology of conventional PNIPAAm exhibited a homogeneous, dense architecture, while

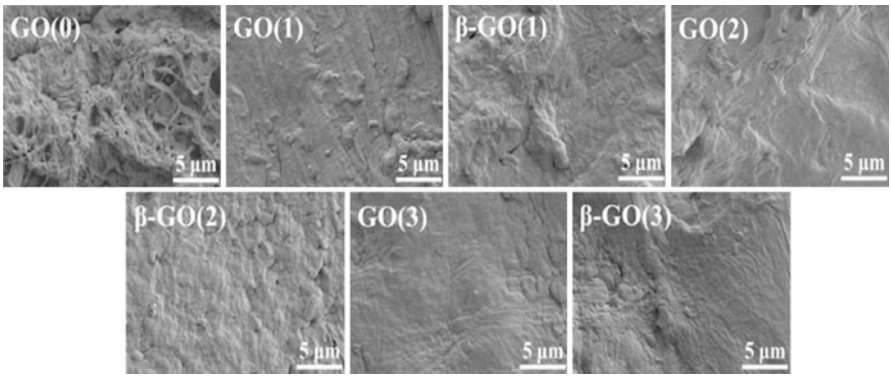

Fig. 26 The SEM micrograph of PVA and GO-loaded PVA hydrogels. (Reprinted with permission from [139] Copyright © 2016, Elsevier)

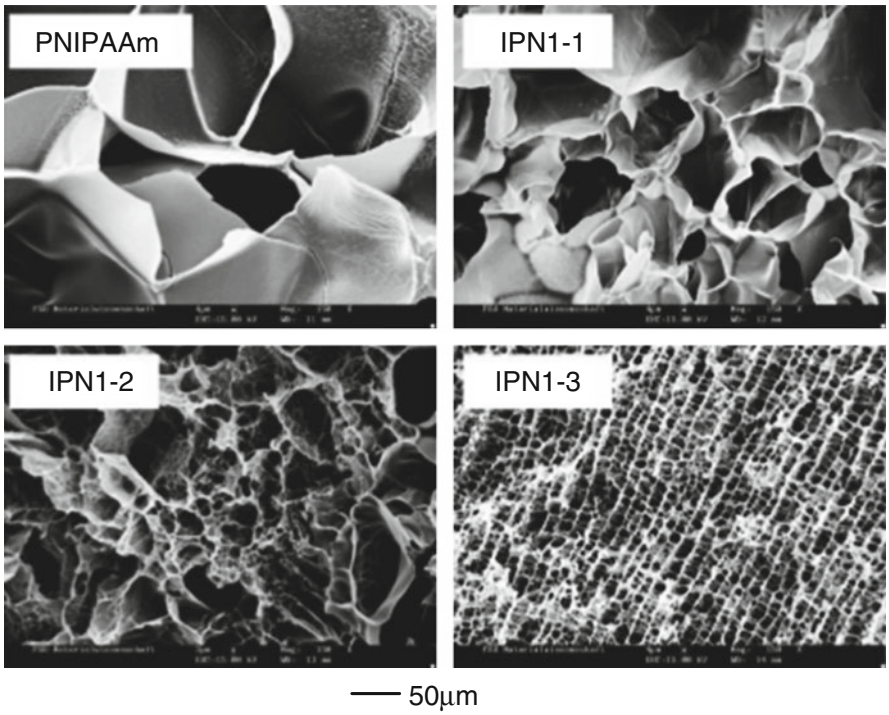

Fig. 27 SEM micrographs of PNIPAAm and semi-IPN1 PNIPAAm/PVA hydrogels. (Reprinted with permission from [140] Copyright © 2008 ActaMaterialia Inc. Published by Elsevier Ltd.)

IPN hydrogels had uneven and porous structures. In addition, the pore size seemed to decrease with increasing PVA content. Because of the fraction of the cross-linked PNIPAAm networks decreased with decreasing the feed ratio of PNIPAAm and

MBAAm from PNIPAAm to IPN1–3, so the supporting force of the cross-linked networks correspondingly decreased, resulting in the shrinking and partial collapse of the bulky networks during the freeze-drying process. In other words, the higher the PVA content, the more pores can be observed. This is possibly ascribed to the increase in the swelling ratio and water content for IPN hydrogels due to the incorporation of hydrophilic PVA, leading to a reduction in the polymer fraction for IPN hydrogels.

Poly(vinyl alcohol)-polyetheretherketone/poly(vinyl alcohol)-β-tricalcium phosphate (PVA-PEEK/PVA-β-TCP) bilayered hydrogels have been investigated by Li et al. [141]. These bilayered hydrogels were developed by freezing-thawing with biomimetic properties for articular cartilage and subchondral bone. The bilayered hydrogel microarchitecture consists of a highly porous and dense structure, and the morphology of the resulting hydrogels was analyzed by scanning electron microscopy (SEM) (Fig. 28). The microstructure of the pure PVA bilayered hydrogels is homogeneous. The typical micrographs of the cross sections of A-K/A-P bilayered hydrogel showed etched features and rough structures with many granules present on the surface. Furthermore, the lower porous layers have an internal three-dimensional structure with lots of micropores on the surface and pore sizes recommended for cartilage tissue engineering scaffolds. These structures indicate that a good bonding exist between the two layers, which is known to be a necessary condition to assure a good integrity and functionality of the osteochondral construction. The lower layer of porous pure PVA bilayered hydrogels had showed a smooth porous network structure, whereas the A-K/A-P was a relatively homogeneous and porous structure with good pore connectivity. The structures of A-K and A-P were not significantly different from the composite bilayered hydrogel, and the formation of the bilayered structure did not affect the pore size, the porosity, and the microstructures.

Zhou and Li synthesized temperature-sensitive poly(*N*-isopropylacrylamide) (PNIPAAm)/poly(ethylene glycol)s (PEGs) hydrogels [142]. The effect of molecular weight (2000–6000) and PEG content on the morphology of these hydrogels were analyzed with scanning electron microscopy. The micrograph revealed that the PEG-modified PNIPAAm hydrogels have more porous networks and the surfaces are looser than those of the conventional hydrogels. In addition, the average pore size of the PEG-modified hydrogels becomes larger with higher-molecular-weight PEGs and higher PEG content.

Comelli et al. investigated the PNIPAAm-PEG hydrogels after solvent immersion and have found interesting results [143]. The hydrogels were immersed in phosphate-buffered saline (PBS) for 14 days at 37 °C and lyophilized after immersion. The resulting polymeric hydrogel morphology was evaluated using scanning electron microscopy (SEM). The SEM micrograph of PNIPAAm-PEG scaffold immersed in PBS is shown in Fig. 29; the scaffold exhibits a macroporous structure, but the pores do not appear to be interconnected, as is commonly observed in polymeric hydrogels.

The morphology of aminated hyaluronic acid-g-poly(*N*-isopropylacrylamide) (AHA-g-PNIPAAm) thermosensitive copolymer hydrogels has been reported by scanning electron microscopy [144]. These hydrogels were synthesized by coupling carboxylic end-capped PNIPAAm (PNIPAAm-COOH) to AHA

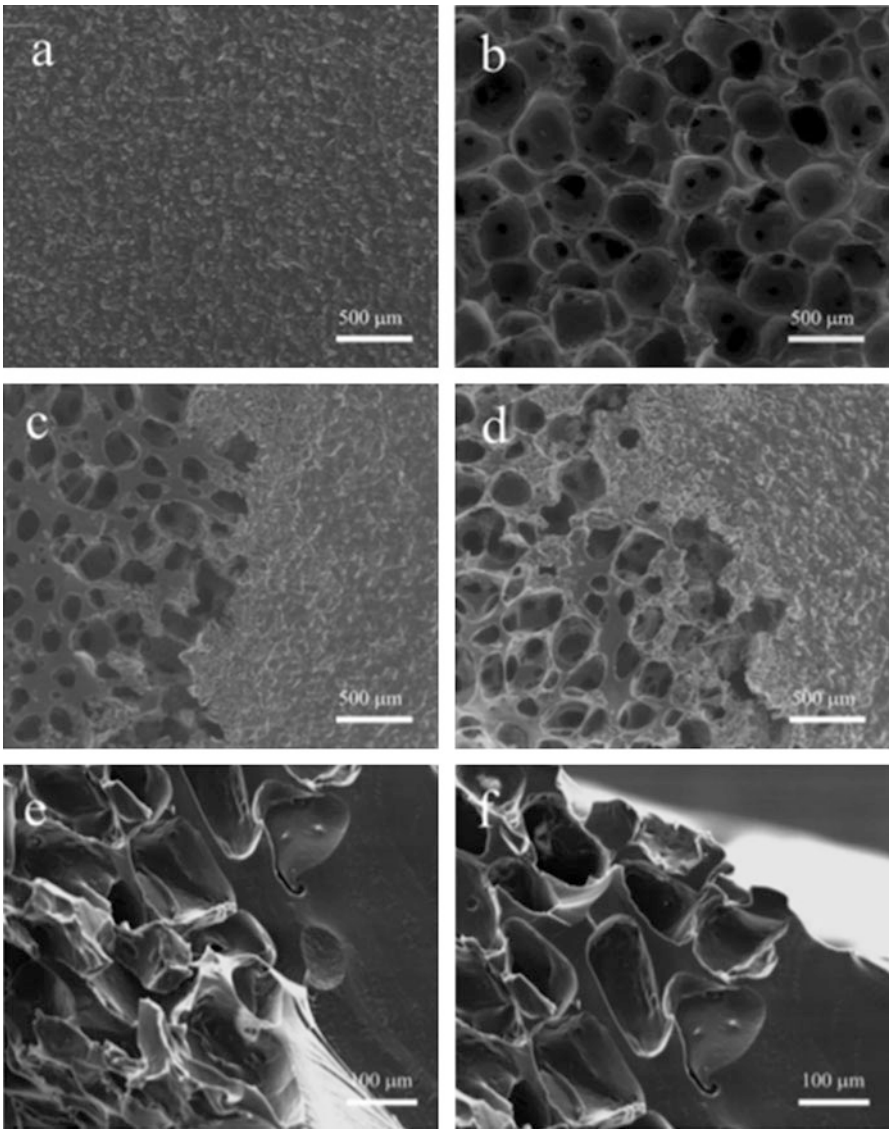

Fig. 28 SEM images of surfaces for PVA-PEEK (A-K) layer (**a**) and PVA- β-TCP (A-P) porous layer (**b**), fracture surfaces for bilayered PVA/PVA (A/A) (**c**, **e**) and PVA-PEEK/PVA-b-TCP (A-K/A-P) (**d**, **f**). (Reprinted with permission from [141] Copyright © 2016, Elsevier)

through amide bond linkages. The SEM images of freeze-dried AHA-g-PNIPAAm hydrogels before and after PBS incubation at 37 °C were shown in Fig. 30. The initial AHA-g-PNIPAAm-28 (28% PNIAAm loaded) and AHA-g-PNIPAAm-53 (53% PNIAAm loaded) copolymer hydrogels displayed a continuous and porous structure. The pore diameter of the AHA-g-PNIPAAm-28

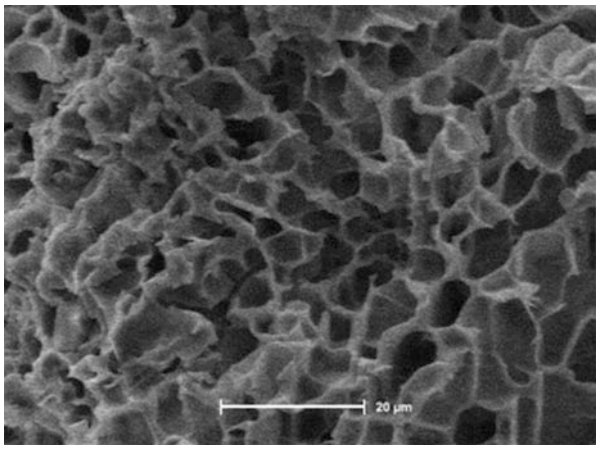

Fig. 29 The morphology of immersed PNIPAAm-PEG scaffold. (Reprinted with permission from [143] Copyright © 2009, Elsevier)

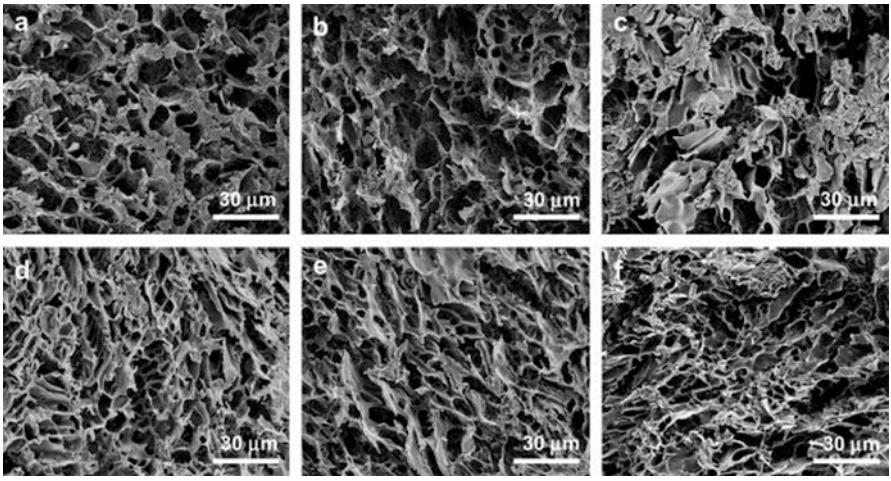

Fig. 30 SEM images to show the internal structures of AHA-g-PNIPAAm-28 (**a**–**c**) and AHA-g-PNIPAAm-53 (**d**–**f**) hydrogels before and after incubation in PBS at 37 °C for different times. (**b**, **e** and **c**, **f**) are 7days and 21days, respectively. (Reprinted with permission from [144] Copyright © 2009, Elsevier)

copolymer hydrogel is in the range of 3–20 μm, compared to a diameter of 1–10 μm pores for the AHA-g-PNIPAAm-53 copolymer hydrogel. This difference in pore size indicates that a higher grafting ratio of PNIPAAm results in the formation of smaller pore diameters and tighter network. After 21 days of incubation, the structure of AHA-g-PNIPAAm-28 hydrogel was partially changed, but there was no significant influence brought to the AHA-g-PNIPAAm-53 hydrogels structures.

The effect of enzymatic degradation on the morphology of AHA-g-PNIPAAm hydrogel was also investigated, and the hydrogels were subjected to enzymatic degradation in 100 U/mL hyaluronidase/PBS at 37 °C for 7 days and 21 days.

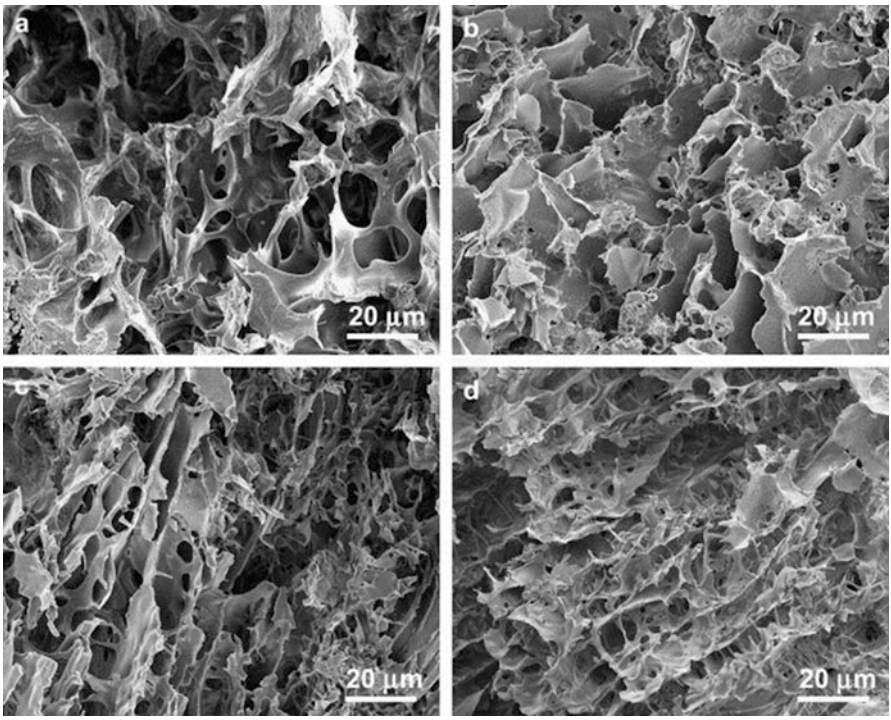

Fig. 31 SEM images to show the internal structures of AHA-g-PNIPAAm-28 (**a** and **b**) and AHA-g-PNIPAAm-53 (**c** and **d**) hydrogels after degradation at 37 °C in 100 U/mL hyaluronidase/PBS for 7days (**a**, **c**) and 21days (**b**, **d**). (Reprinted with permission from [144] Copyright © 2009, Elsevier)

After degradation, the AHA-g-PNIPAAm-28 hydrogel resulted in larger pore diameters (Fig. 31), which is likely due to the mass released from the gel matrix. Compared to AHA-g-PNIPAAm-28, the AHA-g-PNIPAAm-53 hydrogel showed a stable morphological structure during enzymatic degradation, and the pore diameters changed only slightly (Fig. 31), although the weight loss ratios significantly increased from 7days to 21days.

Li investigated the morphology of dry poly(acrylic acid-acrylamide-methacrylate)-amylose hydrogel by using field emission scanning microscopy (FE-SEM). The micrograph showed that the hydrophilic amylose homogeneously dispersed in poly(acrylic acid-acrylamide-methacrylate) hydrogel and gave large porous network structure. This highly porous (pore size ~ 100 μm) structure hydrogel may be suitable adsorbent for crystal violet [145].

Jin et al. have developed spherically shaped semi-interpenetrating network (semi-IPN) poly(*N*-vinylpyrrolidone) (PVP)/poly(acrylic acid) (PAA) hydrogel [146]. The morphology of PVP and semi-IPN hydrogels was investigated by scanning electron microscopy (SEM). The cross-sectional morphology of dried PVP gels swollen completely in two buffer solutions of pH 2.07 and 10.98 are shown in Fig. 32 and

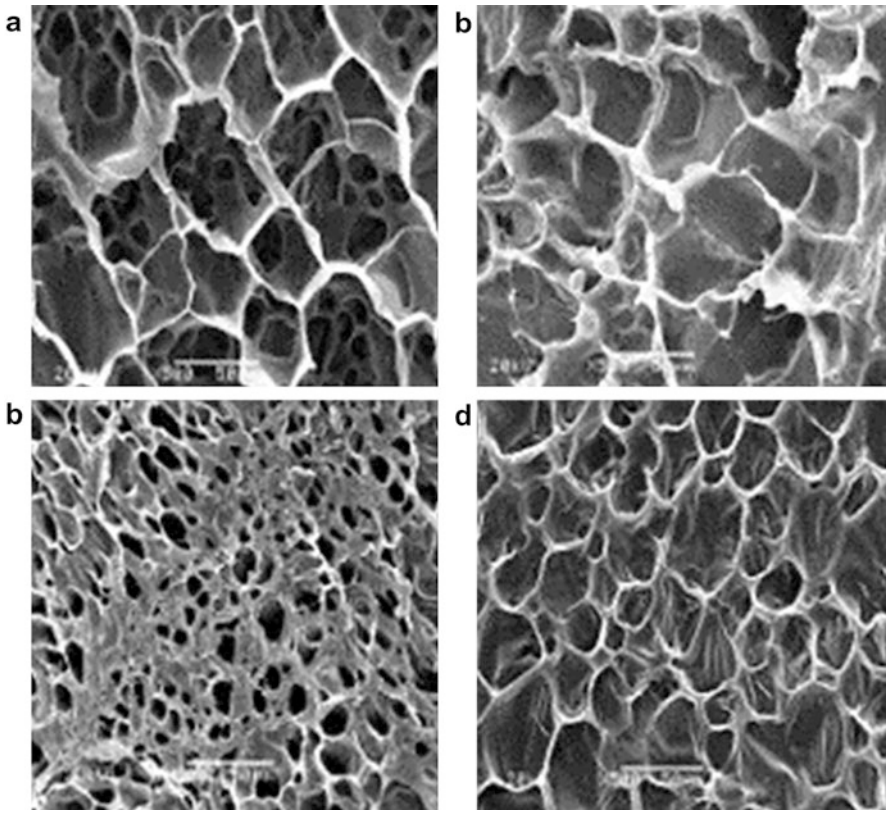

Fig. 32 The SEM micrographs of the hydrogels. (**a**) The PVP hydrogel swelled in buffer solutions of pH 2.07, (**b**) the PVP hydrogel swelled in buffer solutions of pH 10.98, (**c**) the semi-IPN hydrogel swelled in buffer solutions of pH 2.07, (**d**) the semi-IPN hydrogel swelled in buffer solutions of pH 10.98. (Reprinted with permission from [146] Copyright © 2006, Elsevier)

observed that the two hydrogels had similar surface morphology with the larger three-dimensional pores corresponding to similar swelling capacity and very thin pores wall. In contrast, buffer swollen semi-IPN hydrogels had different morphologies. In comparison with the morphologies of PVP hydrogels, the semi-IPN hydrogel had two peculiar features: one was the difference of diameter of the macro pores of the semi-IPN hydrogels swollen in two type solutions. The SEM images shows the smaller three-dimensional net-hole due to the rather compact structure of the semi-IPN hydrogel swollen in buffer solution of pH 2.07 and the larger three-dimensional net-hole of the semi-IPN hydrogel swollen in buffer solution of pH 10.98 (Fig. 32).

The effects of saline water and buffer solutions in poly(vinyl alcohol) (PVA)/poly (acrylic acid) (PAA) hydrogels on morphology have been reported [147]. The PVA/PAA hydrogels was hydrated in saline water at pH 2.8 and pH 5.8, and network structure was observed. A strong effect of the pH was observed in the pore size and

inner structure of hydrogels. At pH 2.8, it displayed irregular pore shapes with variable sizes and at pH 5.8, expanded porous structure due to larger swelling was observed.

7 Conclusion

Morphological characterization of hydrogel reveals essential information regarding the surface of hydrogel as well as the size and shape of the pores in the structure of the hydrogel. Moreover, these characterization information are vital in determining the feasibility of the intended application of the synthesized hydrogel. Morphological properties like porosity of hydrogels, typically analyzed by scanning electron microscope images, are important parameters in deciding the effectiveness of hydrogels in application such as drug delivery system. Not only that, laser scanning confocal microscopy has been successfully used to analyze multilayered hydrogel with oriented structure and in cases where SEM is not viable due to risk of structural collapse during dehydration in SEM technique. As a result, these morphological techniques have been extensively used in designing hydrogels from both cellulose and other biopolymers.

Hydrogels have become a tremendously popular field in research fraternity. The scope it offers far outweighs the trivial disadvantages it brings in applications. Advantages, such as low cost, non-toxicity, hydrophilicity, biodegradability, transparency, and biocompatibility, which biopolymers, particularly cellulose-based hydrogels, bring in, are unmatched and drawing more attention toward this field. In fact, more and more avenues – drug delivery system, water purification adsorbent, chromatographic supports, and biosensors – are being ventured into to unfurl the true prospect of hydrogels. But there are still plethoras of opportunities available to look into for further investigation in the field of cellulose and other biopolymer-based hydrogels. Because of these unrivaled attributes and exponentially growing interest, cellulose-based hydrogel superabsorbents have the potential to become a sustainable and worthy replacement of synthetic polymer-based hydrogels.

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Elastic Modulus Measurement of Hydrogels 27

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Abstract

Hydrogels have been employed for a wide variety of applications, and their mechanical properties need to be modulated based on the applications. In particular, the Young's modulus, or elastic modulus, of hydrogels is a critical property for understanding their mechanical behaviors. In principle, the Young's modulus of a hydrogel can be measured by finding a relationship between a force applied to the hydrogel and the resultant deformation of the hydrogel. On a macroscale, Young's modulus is usually obtained by measuring the stress-strain curves of a hydrogel specimen through the compression method or the tensile method and then finding the slope of the curve. Also, the shear modulus of a hydrogel is measured using a rheometer with parallel plates and then converted into Young's modulus considering Poisson's ratio. On a mesoscale, the elastic modulus can be measured by the imaging-based indentation methods which measure the indentation depth of a hydrogel sample deformed by a static ball indenter on the gel. The measured indentation depth is converted to the Young's modulus of the hydrogel via a contact mechanics model. The mesoscale indentation method and pipette aspiration method are also available. On a microscale, the elastic modulus is usually measured using the atomic force microscopy (AFM)-based indentation method. A hydrogel specimen is locally indented by a sharp or colloidal tip of an AFM probe, and the Young's modulus of the hydrogel is obtained by fitting an appropriate indentation model against the recorded force-distance curves. An appropriate elastic modulus measurement method needs to be chosen depending on the application, length scale and expected elastic property of the hydrogels.

Keywords

Young's modulus · Shear modulus · Atomic force microscopy · Indentation · Rheometer · Compression test

1 Introduction

Hydrogels consist of water-swollen, cross-linked hydrophilic polymers, and they are employed for a wide variety of applications in which their mechanical properties are modulated on purpose [1–4]. In order to understand the basic mechanical or elastic properties related with hydrogels, let's think about a gelatin dessert such as Jell-O. When we enjoy a piece of gelatin dessert and touch it gently with a spoon, the gel changes its shape or deforms. The spoon exerts a force to the gel, which results in the deformation of the gel. When the spoon is removed from the gel, the dessert restores to its initial shape because the gelatin dessert is resilient or elastic. This elastic property or elasticity of the gelatin gel is quantified by its Young's modulus and shear modulus, and these moduli describe the relationships between the stress that the spoon applies to the gel and the strain that the gel shows through deformation.

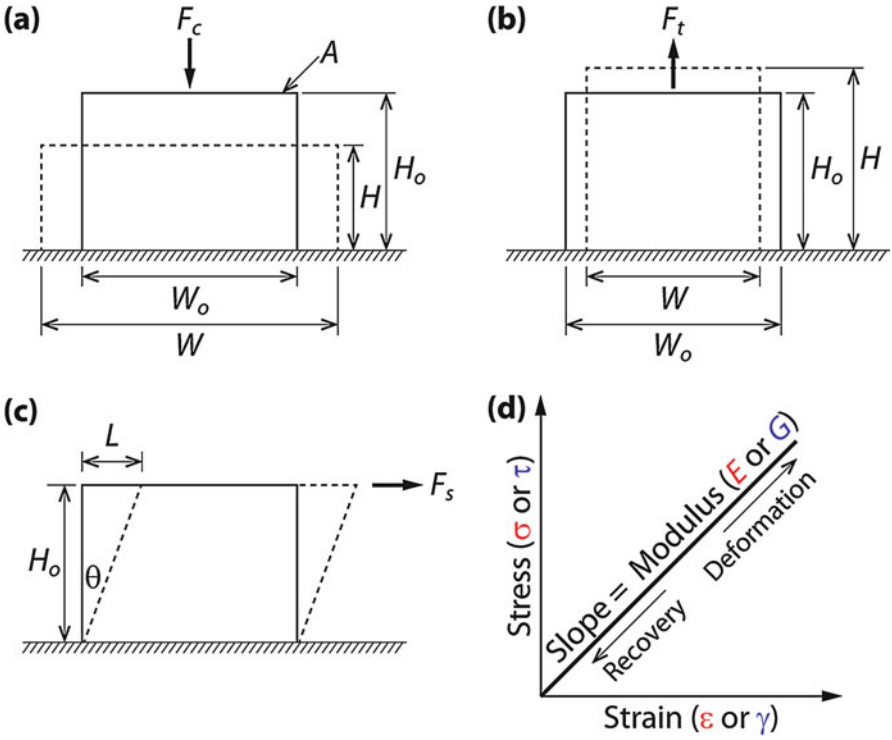

Fig. 1 Measurement of the elastic moduli of a brick-shaped gelatin dessert gel piece of top area A. (**a**) Gel deformation under a compressive force (F_c): the height of the gel decreases from H_o to H while its width increases from W_o to W. The normal stress and strain of the gel are $\sigma = F_c/A$ and $\varepsilon = (H_o - H)/H_o$, respectively. (**b**) Gel deformation under a tensile force (F_t): the height of the gel increases from H_o to H while its width decreases from W_o to W. The normal stress and strain of the gel are $\sigma = F_t/A$ and $\varepsilon = (H - H_o)/H_o$, respectively. (**c**) Gel deformation under a shear force (F_s): the top surface of the gel is displaced by L while its bottom is fixed. The shear stress and strain of the gel are $\tau = F_s/A$ and $\gamma = \theta$ ($= L/H_o$ if θ is small enough). (**d**) Stress-strain curve and elastic modulus. As applied stress increases, the gel deforms more with an increased strain. If the stress is removed, the gel restores to its initial shape due to its elasticity. If the gel is a linear elastic material, its strain-stress curve will be straight, and its elastic modulus will be determined from the slope of the curve

Defining these mechanics concepts needs us to have some assumptions about our dessert. Our piece of dessert is shaped like a brick, and our spoon is flat and large enough to cover the entire top surface of the gel. Now let's press the spoon against the gel (Fig. 1a). Then, normal stress (σ) is defined as the applied compressive force (F_c; unit: N [Newton]) divided with the gel's top surface area where the force is applied (A; unit: m^2), i.e., $\sigma = F_c/A$. The unit of stress is Pa (Pascal; 1 Pa = 1 N/m^2). The definition of stress shows that stress increases either as the applied force increases or as the area decreases. With the applied compressive stress, the gel piece deforms from its original height (H_o) to the decreased height (H), and the resulting normal strain (ε) is defined as the height change ($\Delta H = H_o - H$) per original height,

i.e., $\varepsilon = \Delta H/H_o$. Strain has no dimension because it is a ratio of two length dimensions. Since stress and strain do not contain information on the dimensions of our gelatin gel, they are effective ways to compare compressive force on and resultant deformation of gelatin gel pieces of different sizes.

Now we are about to measure the Young's modulus of our gelatin dessert. In this compression test, we increase the compressive force on the gel while measuring the resultant deformation of the gel. It is easily expected that the strain of our dessert gel will increase as we push it harder with the spoon. Once a curve showing this behavior is obtained, which is called a stress-strain curve, the Young's modulus (E) of the gelatin gel is determined by the gradient of the curve (Fig. 1d). In the case that our dessert is a linear elastic material, its stress-strain curve is a straight line, and its Young's modulus is measured from the slope of the stress-strain curve. If our gelatin gel is made to be soft, it deforms more easily (higher strain) with the same degree of stress, and thus its Young's modulus is low. If the gel is stiffer, it resists deformation more (lower strain), and thus its Young's modulus is high. Therefore, Young's modulus is a measure of the elasticity or stiffness of our gelatin gel.

While being pressed down by the spoon, the gel also deforms in the horizontal direction (Fig. 1a). This lateral deformation is determined by the Poisson's ratio of the gel. Poisson's ratio (ν) is a ratio between the lateral strain and the normal strain of the gel, i.e., $\nu = (\Delta W/W_o)/(\Delta H/H_o)$. In other words, Poisson's ratio illustrates a relationship between the gel deformation in the direction of the applied stress and the deformation in the direction perpendicular to the stress. If our gelatin dessert is incompressible, which means that its volume does not change with applied stress, its Poisson's ratio is 0.5, i.e., $\nu = 0.5$.

Similarly, Young's modulus measurements can be done by stretching our dessert gel, i.e., applying a tensile stress, and Young's modulus is determined in the same way (Fig. 1b). Let's assume that we can attach the spoon to the top of the gel piece (possibly using surface tension or adhesion force) and that the bottom of the gel is fixed on the plate. As we lift the spoon applying a tensile force (F_t) to the gel, the gel is elongated in the direction of the force from H_o to H while its lateral dimension decreases from W_o to W according to its Poisson's ratio. Then, the tensile stress on and resultant strain of the gel are $\sigma = F_t/A$ and $\varepsilon = (H - H_o)/H_o$, respectively. It is expected that the gel will be stretched more as the tensile force increases. Therefore, we can measure a stress-strain curve of the gel by applying a tensile force and then measure the Young's modulus of the gel in this tensile test. It needs to be noted that stress-strain curves from the compressive test and the tensile test can be different.

Now let's change the direction of the stress: we gently place our spoon on the gel, not resulting in normal strain, and then move the spoon in the lateral direction (Fig. 1c). The spoon is assumed again to be attached to the gel. Then, the top surface of the gel moves in the direction of the applied shear force (F_s), while the bottom of the gel is fixed on the plate. Therefore, the gel shows shear deformation, which means that one part of the gel slides past the neighboring part. In this case, the applied stress is shear stress ($\tau = F_s/A$; unit: Pa), and the resultant shear

strain (γ) is quantified by the angle θ shown in Fig. 1c. If deformation is small enough, θ can be equated to a ratio of the lateral displacement of the gel's top surface (L) to the height of the gel (H_o), i.e., $\gamma = L/H_o$. Similar to the compressive and tensile tests, we can obtain a curve of shear stress and shear strain, and the gradient is the shear modulus (G) (Fig. 1d). Again, in the case that the gel is linearly elastic, the curve is straight, and its slope is the shear modulus of the gel. If our gelatin gel is isotropic, which means that the gel's properties do not depend on directions, the measured Young's modulus and shear modulus are related via Poisson's ratio: $E = 2G(1 + \nu)$.

In summary, we can determine the Young's modulus and shear modulus of our gelatin dessert by measuring its stress-strain curves and then interconvert its Young's modulus and shear modulus using its Poisson's ratio. Although very simple (thus not rigorous), the concept of the gel example is applied to the elastic modulus measurements of various types of hydrogel. In the following sections, we briefly review experimental methods to measure the elastic modulus of hydrogels depending on their measurement scale: macroscale (scale larger than ~1 mm), mesoscale (sub-mm scale), and microscale (scale smaller than ~100 μm). We also introduce our recent studies on elastic modulus measurement of alginate gels and polyacrylamide gels.

2 Macroscale Measurements

2.1 Compression Method

A traditionally well-established method for hydrogel elasticity measurement is the compression test [5–7]. In this method, hydrogel samples are usually prepared in a disc form, and they are compressed (either confined or unconfined) with a controlled force while their deformation is measured. Then the applied force and resultant gel deformation are converted to compressive stress and strain. Finally, the Young's modulus of the gel specimen is determined from the slope of the obtained stress-strain curve.

One example introduced here is our recent measurement of the Young's modulus of alginate hydrogels. Alginate gel is a biocompatible hydrogel extracted from brown seaweed [8], and its cross-linking is induced by calcium ions. Depending on the concentration and molecular weight of the alginate, cross-linked alginate gels have different elastic moduli. We tested alginate gels made of two different alginate products (Pronova UP MVG, NovaMatrix [molecular weight: >200 kDa] and Alginic acid sodium salt from brown algae, Sigma-Aldrich [molecular weight: 12–80 kDa]) at concentrations of 0.5%, 1.0%, and 1.5%. Alginate gel disc specimens of 9.7 mm in diameter and 6.2 mm in height were cast using agarose gel molds containing calcium ions, and they were immersed in a calcium solution for further cross-linking. Stress-strain curves of the prepared alginate gel specimens were obtained using Instron 5944 (Norwood, MA; loading rate = 1 mm/min) [9]. Their

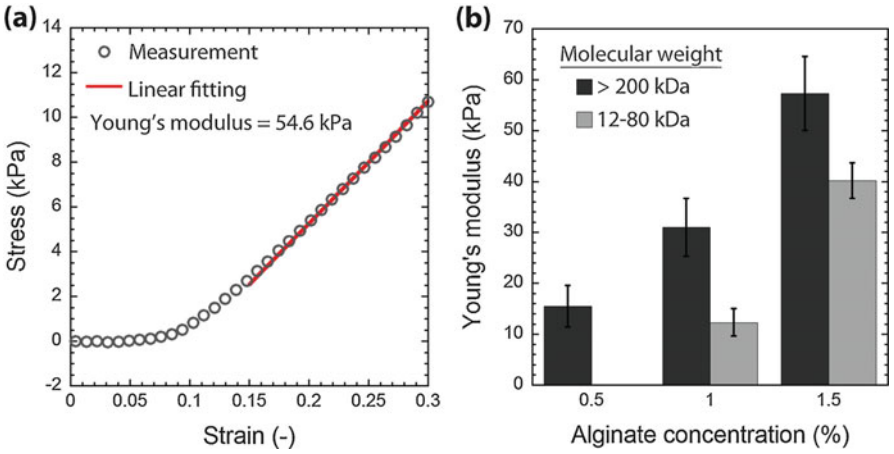

Fig. 2 Young's modulus measurement of alginate hydrogels using the compression method. (**a**) Example of the measured stress-strain data (1.5% Pronova UP MVG alginate). Young's modulus was determined to be $E = 54.6$ kPa from the linear region of the data (red line). (**b**) Measured Young's modulus values of alginate gels increase with the molecular weight and concentration of the alginate. Tested alginate: Pronova UP MVG alginate (molecular weight: >200 kDa) and Sigma-Aldrich Alginic acid sodium salt from brown algae (molecular weight: 12–80 kDa). Error bar: standard deviation (the number of tested specimens per case: 5–6)

Young's modulus values were obtained by fitting a line against a linear region of the data (Fig. 2a), and the Young's modulus of alginate gels was found to increase with the molecular weight and concentration of alginate (Fig. 2b).

The compression method is also applicable to measuring the elastic modulus of hydrogel beads. Ouwerx et al. compressed alginate gel beads and measured their Young's modulus using

$$E = 0.7956 \frac{F_c}{\sqrt{h^3 d}}, \tag{1}$$

where h and d are the deformation and diameter of the beads, respectively [10]. Later, Chan et al. employed a similar compressive approach to measure the elastic modulus of ~2-mm-diameter alginate gel beads [11]. They used the following Hertz theory, which is valid up to 10% strain for hydrogel beads and is similar to Eq. (1):

$$E = \frac{3(1-\nu^2)F_c}{\sqrt{h^3 d}}. \tag{2}$$

The compressive method has an advantage in that the method has no limit on the shape of the hydrogel specimens [2, 4, 12] although cylindrical or disc-like specimens are usually used. In the compression method, preload can be applied to the specimen before stress-strain curve measurements because direct contact between the loading

platens and the specimen is important. Furthermore, lubrication can be necessary between the specimen and the platens because their full contact may cause friction which can result in bulging or shear deformation of the specimen [12].

2.2 Tensile Method

The tensile method is also well-established and widely used for measuring the Young's modulus of hydrogels [6, 13–18]. For tensile testing, hydrogel specimens are prepared in a dumbbell or dog-bone shape, and the ASTM D638 standard is often employed [12, 16, 19]. Because hydrogel specimens are hydrated and usually soft, it is not easy to grip them properly for tensile testing. For this purpose, handles are added to the ends of the specimen using cardboard tabs, double-sided tape and glue, which can facilitate easier clamping and prevent handling damage [3, 12, 14]. Once a clamped hydrogel specimen is stretched at a uniform deformation rate up to a certain level of strain, its Young's modulus is determined by the slope of a certain linear region of the obtained stress-strain curve. Although widely applied, the tensile method has limitations in that the method requires specific geometries of hydrogel specimens, and specimen misalignment can cause measurement errors [4].

2.3 Rheometric Method

As aforementioned, the Young's modulus and shear modulus of a hydrogel can be interconverted with its Poisson's ratio if the gel is isotropic: $E = 2G(1 + \nu)$. Based on this principle, it is possible to measure the elastic modulus of hydrogels by measuring their shear modulus using a parallel-plate-type rheometer [20–23]. A hydrogel specimen is cast between the top and base plates of the rheometer, and the top plate is oscillated at a desired frequency and shear strain (Fig. 3a). As the specimen is twisted and undergoes shear deformation, it exerts resistant shear force on the oscillating plate; and the rheometer measures the shear modulus of the gel based on the relationship between the shear stress applied to the gel and the resultant shear strain of the gel. Since the rheometric method involves shearing a hydrogel specimen, it is important to prevent slip between the hydrogel specimen and the plates.

An exemplary case is our measurement of the Young's modulus of polyacrylamide (PAAM; Bio-Rad, Hercules, CA) gels using a rheometer (AR 1500ex; TA Instruments, New Castle, DE) [24, 25]. The elasticity of the PAAM gel can be modulated by controlling the ratio between its monomer (acrylamide) and cross-linker (bis-acrylamide) [26, 27]. A PAAM gel specimen was cast between the rheometer base plate and a 25-mm-diameter stainless steel plate (Fig. 3a). After 1.5-h-long polymerization at room temperature, the shear modulus of the gel was measured using strain amplitude sweep (1 rad/s, 0.1–10% strain) while evaporation of water was reduced with a humidity chamber. The measured shear modulus was found to be almost constant over the applied strain range (Fig. 3b). Finally, the Young's modulus of PAAM gels was calculated from the measured shear modulus values assuming

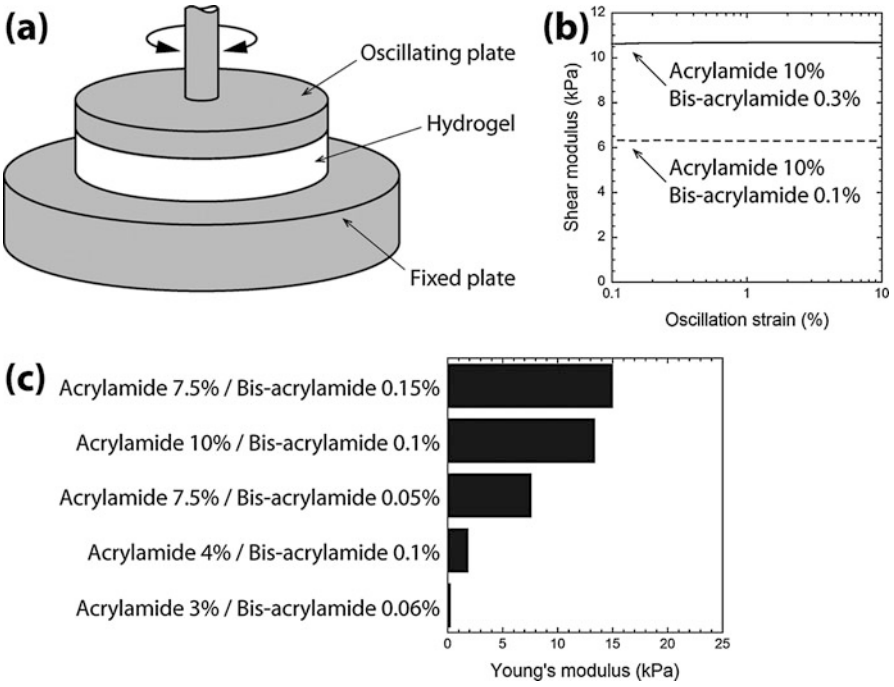

Fig. 3 Rheometric measurement of polyacrylamide (PAAM) hydrogel elasticity. (**a**) Schematic of the rheometric measurement using the parallel-plate-type rheometer. A hydrogel specimen is cast between the parallel plates and twisted by the oscillating top plate. The shear modulus of the gel sample is measured from a relationship between the shear stress applied to the gel and the resistance shear strain of the gel. (**b**) Example shear modulus data of PAAM gels of two compositions. Measured shear moduli were converted to Young's moduli: $E = 18.9$ kPa for PAAM gel of 10% acrylamide and 0.1% bis-acrylamide, and $E = 32.0$ kPa for PAAM gel of 10% acrylamide and 0.3% bis-acrylamide. (**c**) Young's moduli of PAAM gels measured by the rheometric method [24, 25]. The elasticity of PAAM gels depends on their compositions

that the PAAM gels were incompressible ($\nu = 0.5$). As shown in Fig. 3c, PAAM gels showed different Young's moduli depending on their ratios between acrylamide and bis-acrylamide.

2.4 Macroscopic Indentation Method

The macroscopic indentation method measures the Young's modulus of a hydrogel specimen by indenting its surface using an indenter that is smaller than the specimen. This method depends on the tip geometry of the indenter used and the relative dimension of the indenter to the hydrogel specimen [7]. Hemispherical indenters are known to minimize the stress concentration and sample damage. In contrast, flat-ended cylindrical indenters are known to simplify theoretical analysis of the

gel-indenter interaction because the contact area between the indenter and the gel specimen can be assumed to be constant. However, using flat-ended indenters requires indenting the specimen perpendicularly to its surface [18]. For instance, Ross and Scanlon used flat-ended cylindrical indenters with 0.5–4 mm diameters and measured the Young's modulus of agar gels using

$$E = \frac{(1-\nu^2)F_c}{2\delta r}, \tag{3}$$

where δ is the indentation depth of the hydrogel and r is the indenter radius [28]. They found that the elastic modulus value from the indentation method was about 50% higher than that from the compression test.

2.5 Bending Method

It is also possible to measure the elastic modulus of hydrogels based on the gravity-driven bending of cylindrical hydrogel specimens. Peng et al. prepared cylindrical specimens of PAAM gel by pushing the gel out of a syringe pinhead; then they imaged the bent hydrogel specimens [29]. When a hydrogel cylinder was held horizontally, it was deflected downward because of its own weight. Then, the Young's modulus of the hydrogel was measured by fitting a mechanics model against the curvature of the bent cylinder.

3 Mesoscale Measurements

3.1 Microscopy Indentation Method

Conventional microscopy indentation methods for hydrogel elastic modulus measurement consist of the following steps (Fig. 4) [18, 19, 30–37]. First, micron-sized beads are embedded in a hydrogel sample to visualize the gel's top surface, and a sphere or ball indenter of 0.5–1 mm in diameter is placed on the hydrogel in a liquid. The indentation force (F) from the indenter, which is the weight of the indenter in the liquid, deforms the gel surface locally. Then, the beads at the bottom of the indented surface are identified with an optical microscope. After the indenter is removed and the hydrogel has restored elastically, the beads identified in the previous step are focused again. Finally, the indentation depth (δ) of the gel is measured from the displacement of the focal plane of the microscope. The indentation depth can also be measured by measuring the distance between the equator of the ball indenter and the undeformed top surface of the hydrogel and then subtracting this distance from the radius of the indenter [36, 37].

Then, the Young's modulus of the hydrogel is calculated from the indentation force and radius (r) of the indenter, and the indentation depth of the gel, using a proper indentation model, such as the following Hertz model for spherical indenters:

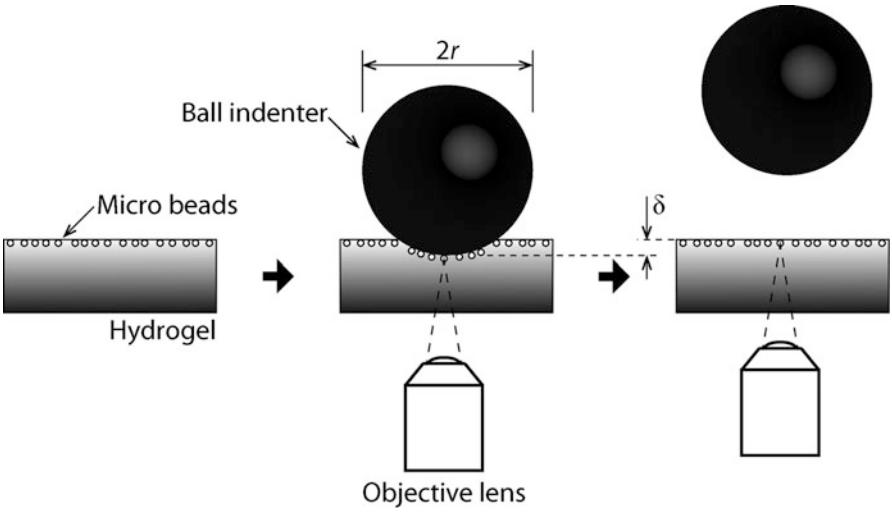

Fig. 4 Schematic of the microscopy indentation method. A hydrogel specimen is prepared with micron-sized beads embedded, and a ball indenter is placed on the specimen. A microbead near the center of the indented gel surface is focused using a microscope, and its vertical location is traced upon removal of the indenter to measure the indentation depth (δ) of the hydrogel. Then, Young's modulus is determined based on the measured indentation depth, the indenter's size ($2r$) and indentation force, and an appropriate contact mechanics model

$$E = \frac{3(1-\nu^2)F}{4\sqrt{r\delta^3}}. \tag{4}$$

It is known that Eq. (4) is valid for the parameter regime of $0 < \delta < \min(0.3r, 0.2h)$ [34, 38] and $a/r < 0.1$ [38–41]. Here, h is the gel thickness, and a is the contact radius between the indenter and the gel. Refer to the work of Long et al. [35] for a detailed discussion on Hertz theory and the effect of hydrogel specimen thickness on the microscopy indentation method.

The microscopy indentation method is cost-effective because it does not require special instruments and it can be easily adopted in research settings with an optical microscope. Also, the method has been validated with tensile measurement [18, 19]. However, the current microscopy indentation method has a limitation that it cannot visualize the deformed surface of hydrogels. Such information is important for understanding gel-indenter interactions and selecting an appropriate contact mechanics model for Young's modulus determination.

3.2 Confocal Microscopy Indentation Method

We recently proposed an improved microscopy indentation method that uses confocal laser fluorescence microscopy and automated image processing

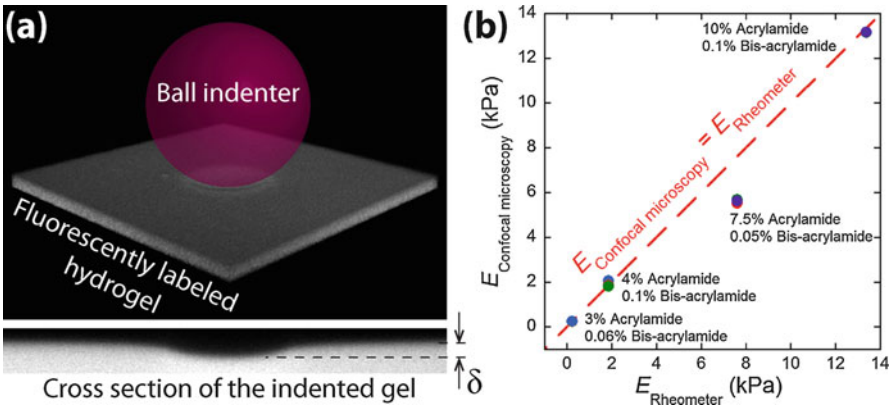

Fig. 5 Confocal microscopy indentation method (reproduced with permission from [24]). (**a**) Schematic of the method. Top: Reconstructed 3D image of a fluorescently labeled PAAM gel specimen indented by a spherical ball indenter. Bottom: Cross-sectional view of the 3D gel image showing the indented surface of the gel. Indentation depth (δ) was determined from this cross section. (**b**) The Young's modulus values of tested PAAM gels compared with those measured with the rheometric method. A good agreement between the two methods validated the confocal microscopy indentation method. The color of the dots indicates different diameters (400, 670, 794, and 1000 μm) and densities (3.84, 7.67, and 14.95 g/cm^3) of five ball indenters. Regardless of different levels of the applied indentation force, the confocal microscopy indentation method resulted in similar Young's moduli for a certain PAAM composition

(Fig. 5a) [24]. Briefly, allylamine particles (Alfa Aesar, Ward Hill, MA) were included in a PAAM gel specimen during gel preparation, and the gel was fluorescently labeled using a fluorescent dye (Alexa Fluor 488; Life Technologies, Carlsbad, CA). Then, a submillimeter-sized ball indenter was placed on the hydrogel specimen immersed in a liquid buffer, and a three-dimensional (3D) image of the indented gel was obtained using a confocal fluorescence microscope (LSM 510; Carl Zeiss, Jena, Germany). The indentation depth was measured by automated image processing of the 3D image using MATLAB (MathWorks, MathWorks, Natick, MA). Finally, Young's modulus was calculated using the contact mechanics model proposed by Dimitriadis et al. [42] because the size of the ball indenters was comparable to the gel thickness.

The confocal microscopy indentation method was tested using four different PAAM gel compositions and five ball indenters of different sizes (400, 670, 794, and 1000 μm) and densities (3.84, 7.67, and 14.95 g/cm^3). All the gel specimens showed an approximate twofold change in the indentation depth responding to increased indentation forces from heavier indenters, but the measured Young's modulus values showed negligible differences (Fig. 5b). Then, the method was validated with the rheometric method, and the measured E values showed good agreement between the two methods (Fig. 5b).

The confocal microscopy indentation method has the following advantages. First, the method does not require indenter removal for indentation depth measurement. Second, the method enables user-independent measurement of the indentation depth based on its automated image processing technique. Third, the method can measure the contact radius between the indenter and the gel from the visualized indented gel profile, which enables selecting an appropriate contact mechanics model. Last, the method can be applied to any kind of hydrogel that can be fluorescently stained for confocal imaging.

3.3 Optical Coherence Tomography-Based Method

Similar to the confocal microscopy indentation method, optical coherence tomography (OCT) was employed for the indentation test in order to image the cross section of indented hydrogel specimens [2, 43, 44]. OCT is an interferometric imaging method that enables 3D and noninvasive imaging of soft materials at a micrometer-level resolution. Therefore, the OCT-based indentation method can measure the indentation depth of a ball indenter into a hydrogel specimen, as well as the thickness and geometry of the specimen. Then, the elastic modulus of the hydrogel sample can be determined based on the obtained dimensions.

3.4 Mesoscale Indentation Method

Because the indentation methods introduced in Sects. 3.1, 3.2, and 3.3 rely on the gravitational force on the ball indenters, they are limited in modulating indentation force and thus local deformation of hydrogels. Instead, a calibrated glass cantilever with a spherical tip of 100–200 μm in diameter was used to indent hydrogels with a controllable indentation force [34, 45–47], which is similar to the atomic force microscopy (AFM)-based indentation method introduced in Sect. 4.1. Especially, Jacot et al. validated the method based on comparisons with the tensile method using PAAM gels [45]. They found that the elastic modulus measured by the mesoscale indentation method was ~20% lower than that by the tensile test. Similar to the macroscale indentation method, mesoscale indenters with a flat-ended tip were also used [48, 49]. This mesoscale method using a spherically tipped glass indenter is cost-effective compared to the AFM indentation method although the two methods are based on similar working principles.

One rather unique method for mesoscale indentation is to utilize a water jet to locally deform the top surface of a hydrogel specimen. Chevalier et al. proposed the water jet indentation method in which a pressurized water jet flow indented PAAM gels [50]. Because the method exerted a hydrodynamic pressure on an area of 0.05 mm^2, which is approximately equivalent to 220 × 220 μm^2, it measured the mesoscale elasticity of the tested gels.

3.5 Magnetic Force-Based Method

In addition to being used as the ball indenter for the indentation methods introduced in Sects. 3.1, 3.2, and 3.3, steel balls can be included in a hydrogel specimen to deform the hydrogel locally. Lin et al. embedded a 0.79-mm-diameter steel ball in DNA-cross-linked PAAM gels and manipulated the ball using a magnetic force to deform the gel locally [51, 52]. Then, the elastic modulus of the hydrogel was measured by relating the linear displacement of the ball which was measured using video microscopy, and the magnetic force exerted to the ball. Considering the diameter of the steel ball used, the method measured the local elastic modulus of the hydrogel on the mesoscale. This magnetic-tweezer-like method has an advantage in that it is a nonintrusive method, but removing the embedded sphere can cause damage of gel samples. Also, it requires a calibration step to evaluate the magnetic force applied to the steel ball.

3.6 Pipette Aspiration Method

The pipette aspiration method pinches a small portion of a hydrogel specimen by applying a negative pressure to the sample with a glass micropipette. Then, the Young's modulus of the hydrogel is determined by a relationship between the applied pressure and the hydrogel's aspirated length into the pipette. This relationship depends on the Poisson's ratio and thickness of the gel specimen, and the relative micropipette wall thickness determined by the inner and outer radii of the used pipette [53, 54]. Recently, Buffinton et al. compared the pipette aspiration method (contact area of ~1 mm^2) with the macroscale compression method and the mesoscale indentation method (contact area of ~0.1 mm^2) using PAAM gels [54]. They observed differences in the measured elastic moduli among these methods, which appears to be because these methods imposed different loading conditions to the hydrogel.

The pipette aspiration method can also be applied to hydrogel beads. Kleinberger et al. aspirated alginate gel beads using micropipette aspiration and calculated the Young's modulus of the hydrogel spheres using

$$E = \Delta p \frac{3R}{2\pi l \varphi}, \tag{5}$$

where Δp is the pressure difference applied across the gel sphere, φ is the wall function depending on the wall thickness of the used pipette, l is the length of the gel portion aspirated into the pipette, and R is the inner radius of the pipette [55]. Equation (5) requires a thin-walled pipette having a small inner diameter compared to the gel bead diameter.

Related to the pipette aspiration method, the pipette-based method of Wyss et al. is noteworthy [56]. They used tapered micro-capillaries to squeeze whole PAAM gel spheres and determined the elastic modulus of the gel based on a relationship

between the deformation of the gel spheres and the applied pressure difference across the gel spheres. Their method was validated with the compression method, and the Young's modulus values measured in the pipette measurement were a little higher than those measured in the bulk measurement.

4 Microscale Measurements

4.1 AFM Indentation Method

Indentation tests using atomic force microscopy (AFM) have been widely used to measure the elastic modulus of various hydrogels [15, 23, 45, 57–62]. Typically, a hydrogel specimen is indented in a liquid by the sharp or spherical tip of an AFM probe with a predetermined trigger force and probe speed (Fig. 6a). A force-distance curve is recorded and converted to a force-indentation depth curve, and then the Young's modulus of the hydrogel is estimated by fitting a proper contact mechanics model (e.g., Hertz model and Sneddon model) against the curve (Fig. 6b). Here, the Sneddon model for spherical indenters is

$$\begin{aligned} F &= \frac{E}{2(1-\nu^2)}\left[(a^2+r^2)\ln\left(\frac{r+a}{r-a}\right)-2ar\right], \\ \delta &= \frac{1}{2}a\ln\left(\frac{r+a}{r-a}\right), \end{aligned} \tag{6}$$

and it is known to be more robust for deeper indentations than the Hertz model, Eq. (4) [63–65]. In this step, AFM post-processing software such as AtomicJ [66] can be used.

For reliable application of the AFM indentation method for hydrogel elasticity measurement, it is critical to know how precise, accurate and repeatable the method is (refer to our summary of previous studies on evaluation of the precision and accuracy of AFM indentation [25] and also Ref. [15, 23, 61]). For this purpose, we recently evaluated the precision, accuracy and repeatability of the AFM indentation method by repeating AFM indentation tests on the same PAAM gels and by comparing the AFM indentation results with rheometric measurements (Fig. 6c) [25]. All AFM indentation tests were conducted in a liquid buffer using MFP-3D-BIO AFM (Asylum Research, Santa Barbara, CA) and probes with a glass bead tip (nominal spring constant = 0.06 N/m; nominal tip diameters = 5 and 12 μm). Force mapping was performed on each hydrogel specimen to obtain multiple force-distance curves.

The precision of the AFM indentation method was evaluated using the relative standard deviation (RSD) of the Young's modulus (E) values from force mapping ($\mathrm{RSD}_E = \sigma_E/m_E$), assuming that the gel samples were homogeneous. Here, m_E and σ_E are the average and standard deviation of the E values, respectively. The measured RSD_E was 1.1–4.6%. Because the RSD_E of the rheometric measurement was 2.1–20.7%, the AFM indentation method appeared to have better precision.

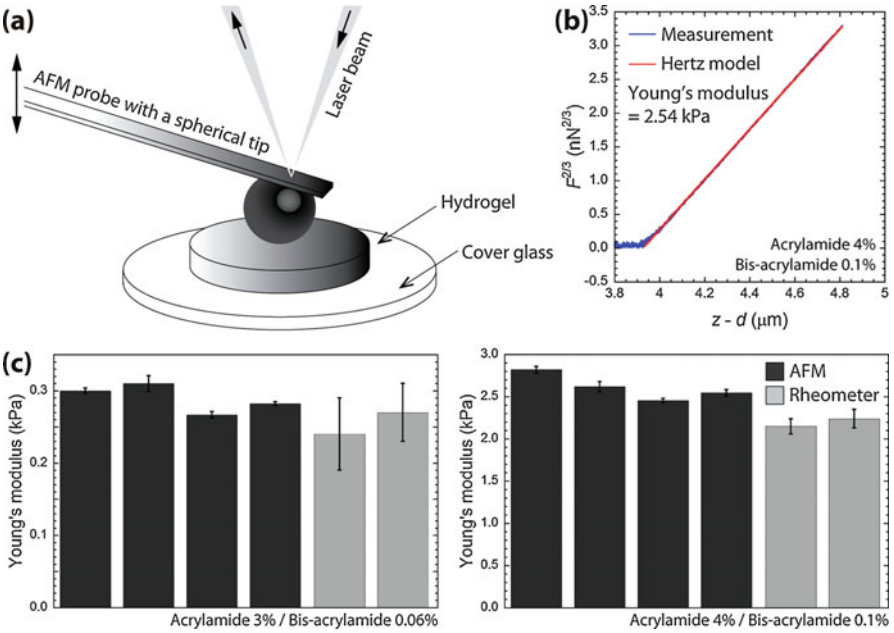

Fig. 6 Atomic force microscopy (AFM) indention for elastic modulus measurement of hydrogels. (**a**) Schematic of the AFM indentation test using a colloidal probe on a hydrogel sample fixed on a cover glass in a liquid (figure not to scale). Once the spherical tip of the AFM probe is engaged on the gel specimen, the probe is lowered to indent the gel and then retracted. Laser beam enables measuring the deflection of the probe. The indentation force from the tip and the indentation depth on the gel are measured from the spring constant, deflection and vertical displacement of the probe. (**b**) Exemplary force (F)-indentation depth ($z-d$) curve of AFM indentation (PAAM gel of 4% acrylamide and 0.1% bis-acrylamide) [25]. Here, z and d are the vertical displacement and deflection of the AFM probe, respectively. The Hertz model, Eq. (4), was fitted against the approach part of the curve as shown by the red line, and the Young's modulus of the gel was measured to be $E = 2.54$ kPa. Indentation condition: probe speed = 1 μm/s, trigger force = 6 nN, nominal spring constant of AFM probe = 0.06 N/m, and tip radius = 5 μm. (**c**) Repeatability and precision validation test results of the AFM indentation method [25]. Tested specimens are PAAM gels of 3% acrylamide/0.06% bis-acrylamide and 4% acrylamide/0.1% bis-acrylamide. Compared with the rheometric method, the AFM indentation method showed similar repeatability (changes in the average E values) and better precision (a ratio of the standard deviation to the average value of E) than the rheometric method. Error bar: standard deviation (from about 120 indentation curves for the AFM indentation measurement and from more than three measurements for the rheometric measurement)

For accuracy and repeatability evaluation, we measured the spatially averaged E value of each gel sample at random time intervals. The accuracy of the AFM indentation method was quantified by comparing the $m_{\bar{E}}$ value of the method with that of the rheometric method. Here, $m_{\bar{E}}$ is the average value of the m_E values from repeated sets of indentation tests. The $m_{\bar{E}}$ ratio of the AFM indentation method to the rheometric method was 0.67–1.19, which indicates that the two methods showed reasonably good agreement.

The repeatability of the AFM indentation method was quantified by using the RSD of the m_E values ($\mathrm{RSD}_{\bar{E}} = \sigma_{\bar{E}}/m_{\bar{E}}$). Here, $\sigma_{\bar{E}}$ is the standard deviation of the m_E values. Because the $\mathrm{RSD}_{\bar{E}}$ was measured to be 2.6–6.0%, we found that the AFM indentation method was repeatable for the examined PAAM gel samples. To sum up, we have confirmed that the AFM indentation method is repeatable with good precision when conducted carefully.

It needs to be emphasized that the quality of the AFM indentation tests is dependent on experimental conditions and data analysis methods. Experimental conditions include *in situ* calibration of the AFM probe spring constant, the geometry and size of the AFM probe tips, sample fixation, and indentation parameters such as probe speed and trigger force. For instance, spherical tips are known to be better for consistent elasticity measurements than sharp tips [42, 65, 67, 68]. Also, it is important to choose a proper contact mechanics model depending on the tip geometry of the AFM probes and the thickness, properties and deformation of the hydrogel samples [60, 69, 70]. Although the AFM indentation method is a versatile tool for probing the mechanical properties of hydrogels, the method is low throughput because of its time consumption, and it can be challenging to determine the contact point between the probe tip and the sample because of their adhesive interactions [71].

4.2 Magnetic Force-Based Method

Similar to the mesoscale method of applying a magnetic force to a sphere embedded in a hydrogel (see Sect. 3.5), Chippada et al. embedded nickel needles with a dimension of $10 \times 1 \times 1\ \mu m^3$ in PAAM gels and applied a magnetic force or torque to the needles using a magnetic manipulator [22, 72]. The two-dimensional translations and rotations of the needles were measured using video microscopy, and the forces and torques on the needles were calculated using finite element analysis (FEA) simulations. Therefore, they could measure the local elastic modulus of the PAAM gels on a microscopic scale. It needs to be noted that in this method, the bulk elastic property of hydrogels can be affected by the inclusion of solid microneedles.

4.3 MEMS-Based Method

Microelectromechanical systems (MEMS) technology can be used to measure the elastic modulus of tiny hydrogels. One example is force-feedback MEMS microgrippers. These grippers could compress micrometer-sized alginate gel beads of 15–25 μm in diameter and thus measure the Young's modulus of the gel spheres [73]. Another application of MEMS is to measure the elastic property of hydrogels using MEMS resonant sensors [74]. These MEMS-based methods have an advantage in that they can measure the microscopic elasticity of hydrogels in similar ways to the macroscopic methods, but their adaptation may be limited by the fact that the methods require resources and expertise for MEMS fabrication.

5 Conclusion

The elasticity of hydrogels refers to their capability to deform instantly, responding to a mechanical loading, and then to restore upon removal of the loading. This elastic behavior of hydrogels is described by their Young's modulus, and this elastic modulus is a criterion of selecting a hydrogel material depending on the need. Currently various experimental methods are available for the measurement of hydrogels' elastic modulus, and this review chapter has categorized them into three different scales: macroscale (1–10 mm order scale), mesoscale (sub-mm order scale), and microscale (10–100 μm order scale). The macroscale methods summarized in Sect. 2 are appropriate for measuring the bulk elastic modulus of homogeneous hydrogel materials, but these methods have drawbacks in that they require separately prepared hydrogel specimens of relatively large volumes, and they cannot measure the elastic modulus distribution of hydrogels. In contrast, the microscale methods reviewed in Sect. 4 are advantageous in that they can probe the local elastic modulus at various points on an inhomogeneous hydrogel specimen of relatively small volume, and hydrogel specimens can be kept hydrated easily in these methods. However, these microscale methods usually require complicated equipment of high cost. The mesoscale methods introduced in Sect. 3 fill the spatial scale between the macroscale methods and the microscale methods with reasonable requirements. Regardless of the pros and cons of these methods, however, it needs to be kept in mind that one should choose an appropriate elastic modulus measurement method depending on the application, dimension and expected property of the hydrogel, and that it is ideal to measure the elastic modulus of the hydrogels under conditions that are as similar as possible to the *in situ* condition of their application.

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Part IV

Applications of Biocompatible Hydrogels

Strategies in Improving Properties of Cellulose-Based Hydrogels for Smart Applications

28

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Abstract

Hydrogels are three-dimensional polymeric networks that are able to absorb and retain large volumes of water. Chemical or physical crosslinks are required to avoid dissolution of the hydrophilic polymer chains into the aqueous phase. Because of their sorption capacity, super absorbing hydrogels have been extensively used as water-retaining devices, mainly in the field of personal hygiene products and in agriculture. Moreover, in recent years, the possibility to modulate their sorption capabilities by changing the external conditions (e.g., pH, ionic strength, temperature) has suggested their innovative application as smart materials, drug delivery devices, actuators, and sensors. The presence of the polyelectrolyte NaCMC in the hydrogel network provides a Donnan equilibrium with the external solution, thus modulating material's sorption capacity in relation to the external solution ionic strength and pH. An important focus of the research in this field is the material's biodegradability. This material was obtained by chemical crosslinking of cellulose polyelectrolyte derivatives, carboxymethylcellulose (CMC) and hydroxyethylcellulose (HEC), using small difunctional molecules as crosslinkers (divinyl sulfone, DVS) which covalently bound different polymer molecules in a 3D hydrophilic network. Among the biopolymers, cellulose is of special interest due to its abundance and, hence, easy availability. It is easily derivatized to different cellulosics which can be used to obtain functionalized hydrogel beads for ion exchange and affinity chromatography. Various cellulose derivatives having nitrogen or sulfur-containing groups have been prepared, and their metal ion absorption behavior has been examined. Metal ions are reported to partition between cellulosics and liquid phase. However, the use of cellulose as membrane material is not fully realized due to low stability and poor interactions in water. These drawbacks can be improved by crosslinking, radiation grafting, and surfactant adsorption. In the current chapter, we have focused on the smart applications of cellulose-based hydrogels including drug delivery systems, absorption behavior, and swelling mechanism and their prospects.

Keywords

Hydrogel · Cellulose · Super absorption · Smart properties · Drug delivery

1 Introduction

Natural cellulosic materials have a wide variety of complex components. Cellulose, hemicellulose, and lignin are important components of natural lignocellulosic materials which comprise the main component of cell walls of plants. Cellulose molecules determine the cell wall framework, and pectin is located between the cellulose microfilaments of the cell wall, while cellulosic materials contain rich cell wall protein, pigment, and ash. In the research and development of cellulose-based hydrogels, it is important to understand the chemical composition and structure of natural lignocellulosic materials and characteristics of each component and also the interrelationships between various components in order to achieve suitable and desirable final characteristics and functional properties.

This chapter discusses properties of cellulose polymers, those that are responsible for preparing cellulose-based hydrogels. The chapter further describes the utility of such cellulose-based hydrogels for various smart applications.

1.1 Physicochemical Properties of Hydrophilic Polymers

Hydrophilic polymers are able to absorb liquids and swell with no dissolving, showing that physical or chemical crosslinks are available inside the macromolecular chains [1]. The network of the polymer resulting from the crosslinks swells in the solvent. The swelling is totally offset by the retractive, elastic force exerted by the crosslinks. The resulting semisolid solution of the water and polymer at equilibrium is called a hydrogel.

The gelling agents for the cosmetic and pharmaceutical applications can be classified into organic and inorganic substances on the basis of the nature of the colloidal phase. One of the examples of inorganic agents is clay that has a lamellar structure and can be highly hydrated. Clays have flat surfaces of particles and are negatively charged, but the edges are positively charged [2]. The content of water in the hydrogel depends on the conditions of the environment, for example, pH, temperature, and ionic strength of the water solution, and also depends on the structure of the network of the polymer. The importance of the swelling ratio of the hydrogel is due to be evaluated for given conditions of the environment because it is effective on the mechanical, optical, surface, diffusive, and acoustic properties of the hydrogel. Hydrogels are theoretically beneficial for the elaboration of smart devices such as artificial muscles, valves, and substrates for controlled drug release. The first invented hydrogel has been based on poly hydroxyethyl methacrylate (PHEMA) that was developed by Otto Wichterle in the 1950s and is used as soft contact lenses [3]. Since then, major improvements have been done through obtaining novel hydrogels, based on natural, synthetic, or hybrid polymers [4]. By association of two polymers, gelation or precipitation can occur. The new generation of hydrogel products has been developed for special applications as a water

absorbent such as underwater devices, personal hygiene goods, and water reservoirs for dry soils or for biomedical applications such as lubricating surface coatings, soft contact lenses, phantoms for ultrasound imaging, wound healing dressings, controlled drug release devices, three-dimensional cell culture substrates, cell immobilization islets, bioactive scaffolds for regenerative medicine, and three-dimensional cell culture substrates [5].

1.2 Cellulose as Hydrophilic Polymers

Cellulose is the richest natural biopolymer [6]. There are long chains of anhydro-D-glucopyranose units (AGU) in its structure, and with each molecule of cellulose, there are three groups per AGU with the exception of the terminal ends [7]. Cellulose is not soluble in most of the solvents and especially in the water [6]. The cause of poor solubility is because of the intermolecular hydrogen bonding and strong intramolecular between the individual chains [7]. Despite the poor solubility of cellulose, it is used in a wide range of the applications such as netting, paper, coatings, composites, upholstery, packing, etc. [8]. The morphology of cellulose has a great impact on its reactivity, and the hydroxyl groups located in the amorphous sections react readily and are highly accessible, but those in crystalline sections with strong interchain bonding and close packing can be completely inaccessible. For the cellulose derivatives, different scores can show various characterizations considerably in terms of viscosity, hydration, molecular weight, and solubility; therefore, various scores can be applied to various goals [9].

Cellulose is the most plentiful natural polymer of glucose that is found as the main ingredient of natural fibers and plants such as linen and cotton. Bacterial cellulose (BC) or microbial cellulose is chemically same to plant cellulose (PC), but there are some differences in physical structure and various macromolecular structures. The insolubility in water and the rest of the solvents and the high crystallinity of the cellulose in both PC and BC is due to the units of the glucose that are held together via 1,4-β-glucosidic linkages [10]. This amount is more than 60% for BC and 40%–60% for PC. The nanosized fibers are the result of BC biosynthesis that is smaller than PC fibers around two orders. Therefore, BC cellulose displays an ultrafine and unique fiber network with larger flexible strength and more water holding rather than PC.

Additionally, BC is entirely pure disparate PC that is associated with the rest of the biogenic compounds like pectin and lignin. Hence, whenever BC is applied by bacteria, PC needs more refinement and some reformation. Meanwhile, the further modification of BC could be done using ex situ or in situ approach as shown in Fig. 1 in order to develop desirable form and properties using various types of additives including nanoparticles such as conductive polyaniline [11].

Cellulose and derivatives of cellulose are nature-friendly and can be degraded by various fungi and bacteria available in the water, air, and soil that can synthesize special enzymes such as cellulases [12].

The most important reason for the huge use of cellulose-based devices in biomedical applications is the high biocompatibility of cellulosics, cellulose, and

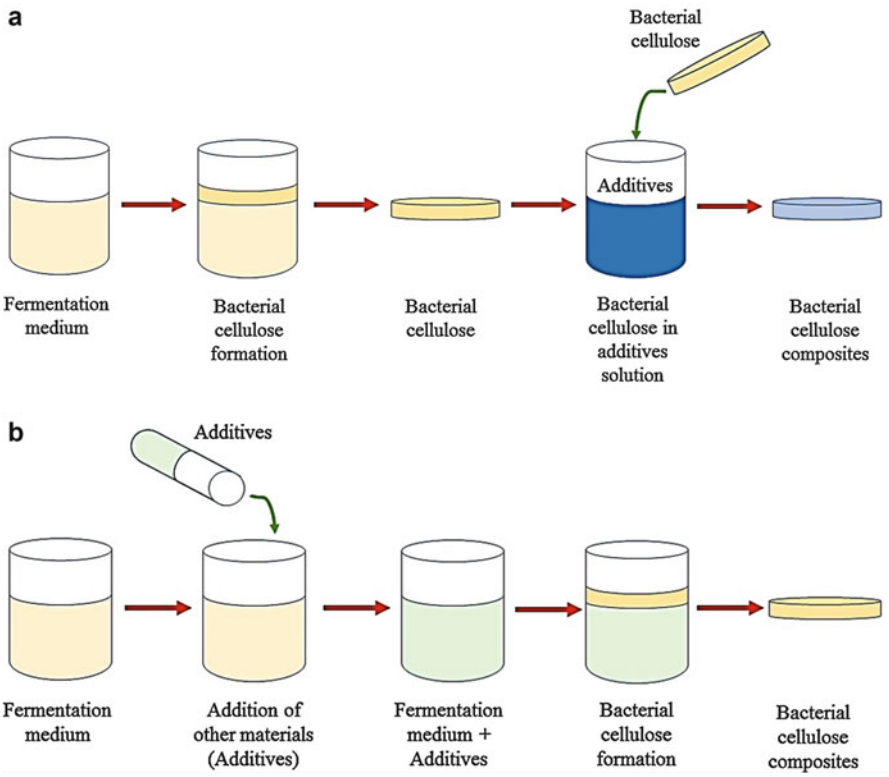

Fig. 1 Modification of bacterial cellulose using (**a**) ex situ and (**b**) in situ method

cellulase-mediated. Truly, due to the disability of cells to synthesize cellulose, resorption of cellulose in human and animal tissues does not occur. Martson et al. showed that an implant based on cellulose sponge appears to suffer a slow degradation in the subcutaneous tissue of the rat [13].

1.3 Water-Soluble Cellulose Derivatives

The water-soluble derivatives of cellulose can be reached by etherification of the cellulose that contains the reaction of the organic species like ethyl and methyl units with hydroxyl groups of cellulose [14]. So as to reach soluble derivatives of cellulose, the ordinary number of etherified groups of hydroxyl in a glucose unit or degree of substitution can be controlled to an assured level. Cellulose-based hydrogels can also be created by crosslinking the aqueous solutions of cellulose ethers, for example, hydroxypropyl methylcellulose (HPMC), methylcellulose (MC), hydroxyethyl cellulose (HEC), ethyl cellulose (EC), and sodium carboxymethylcellulose (NaCMC). Due to the low cost and nontoxicity of such polymers, all of them have an extended application as emulsifying agents or thickeners in the cosmetics and pharmaceutical industries [15]. NACMC is just the polyelectrolyte

that presents sensitivity to ionic strength and pH variations, and so it is a smart cellulose derivative. Actually, using NACMC in a cellulose-based hydrogel makes it a double effect on the swelling property and that is because of electrostatic charges attached to the network [16].

Increasing in the swelling is due to the electrostatic repulsion recognized among charges of the same sign that makes the chains of the polymer force to a more stretched state rather than those found in a neutral network [17]. More than this, due to the Donnan effect, the counterions which exist in the gel induce more water to enter the network by macroscopic electrical neutrality. Making the gel sensitive to different ionic strength or pH is because of different concentrations of mobile counterions among the external solution and gel, which is described by Donnan contribution to the osmotic pressure. The elaboration of superabsorbent hydrogels with a smart behavior is due to the polyelectrolyte nature of NaCMC [18].

2 Application of Cellulose-Based Hydrogels

Extensive employment of hydrogel-based products in a number of industrial and environmental areas of application is considered to be of prime importance. As expected, natural hydrogels are gradually replaced by synthetic types due to their wide varieties of raw chemical resources, higher water absorption capacity, and durability. The responsiveness of some cellulosics to variations of external stimuli, large access, low cost, and biocompatibility of cellulose makes the hydrogel precursor materials. This section lays on some of the applications of cellulose-based hydrogels in the range of the traditional use of hydrogels as water absorbents to more inventive biomedical applications.

2.1 Uses of Cellulose and Cellulose Derivatives

2.1.1 Sodium Carboxymethylcellulose

Figure 2 shows the molecular structure of carboxymethylcellulose which is often used as its sodium salt, sodium carboxymethylcellulose. It is a soluble and cheap polyanionic polysaccharide derivative of cellulose that has been employed as an emulsifying agent in the cosmetic and pharmaceutical industry.

This polymer has many critical properties such as stabilizer, thickener, film-former, and a binder [19]. One of its applications in biomedicine after a surgical procedure is to prevent epidural scar and soft tissue adhesions. Another of its applications includes the therapeutic application of the superoxide dismutase enzyme (SOD), as hydrogels of CMC carrying the enzyme for its controlled release and also as water absorbents in treating edemas [20].

Therapeutic use of SOD enzyme is limited by its fast clearance from the blood-stream and inactivation by its own reaction product, i.e., hydrogen peroxide. To use the NaCMC in preparation of the semi-interpenetrating network of polymer, glutaraldehyde can be used as a crosslinker [21].

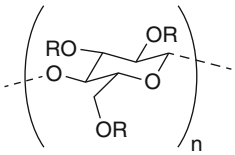

Fig. 2 Molecular structure of carboxymethyl cellulose ($R = H$ or CH_2CO_2H)

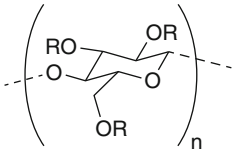

Fig. 3 Molecular structure of hydroxypropyl cellulose ($R = H$ or $CH_2CH(OH)CH_3$)

2.1.2 Hydroxypropyl Cellulose

Hydroxypropyl cellulose is an ether of cellulose which had been hydroxypropylated using propylene oxide. The hydroxyl groups in the repeating glucose units have been forming $–OCH_2CH(OH)CH_3$ groups as shown in Fig. 3. It is a pH insensitive, water soluble, and nonionic cellulose ether. Its application is the film coating, tablet binding, thickening agent, and modified release. To control the release ratio of a water-soluble drug-like oxprenolol hydrochloride, solid dispersions including a polymer blend can be used. Therefore, there is a direct relationship between the release ratio of drug solution and its interaction with the polymer. The graft copolymers can be considered of great interest as direct compression excipients due to their different chemical structure and composition; they showed differences in viscoelastic properties that revealed an interesting range of possibilities for use in drug delivery formulations [22]. The use of this kind of graft copolymer in a formulation could improve the controlled release properties.

Furthermore, non-crosslinked graft copolymers of hydroxypropyl methacrylate on both hydroxypropyl starch and HPC offer interesting characteristics as controlled release matrices. The graft copolymers can stand alone as an effective matrix for tablets designed for drug delivery systems [23].

2.1.3 Oxycellulose

In oxidized cellulose or oxycellulose, some of the groups of the terminal primary alcohol in the glucose have been shifted to groups of carboxyl. Thus, this derivative of CMC is certainly a synthetic polyanhydrocellobiuronide that includes 25% groups of carboxyl that are very weak and have high solubility in the solutions [24]. The products with fewer carboxyl groups are more desirable in the products. Cotton or gauze as an oxidized cellulose is soluble in dilute alkalis but insoluble in acids and water. These products can swell and become gelatinous in the high dilute alkaline solutions. In contact with blood, it swells and become slightly, so forms a dark brown gelatinous product. This capability makes it an appropriate product to use in different surgical procedures [25]. This product also can be used as novel-forming systems because of its dispersion that might be combined with the rest of cosmetic and pharmaceutical adjuvants due to their dispersion in the water. One of the main

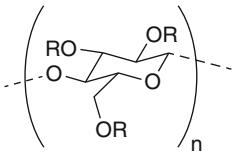

Fig. 4 Molecular structure of methylcellulose (R = H or CH_3)

properties of such products is that basic bioactive compounds liquid (nonvolatile or volatile) acidic, neutral, and a wide variety of solid (amorphous or crystalline) can be loaded into them, so it becomes possible to generate substantive sustained or controlled release formulations in the development of different pharmaceutical, cosmetic, agricultural, and consumer products. Oxidized cellulose dispersion uses in sunscreen spray, anti-acne cream, anti-fungal cream, and anti-acne lotion [26].

2.1.4 Methylcellulose

Methylcellulose is synthetically produced by heating cellulose with caustic and treating it with methyl chloride. The hydroxyl residues are replaced by methoxide (-OCH3 groups) as shown in Fig. 4. Methylcellulose resembles cotton in appearance and is tasteless, neutral, inert, and odorless. It is not soluble in the organic solvents, but it can be swelled in the water and produces a viscous, clear to the opalescent and colloidal solution. Therefore, dilution of aqueous liquids containing methylcellulose can be with ethanol. Their solutions are stable at higher than the range of pH (2–12) without any superficial change in viscosity.

Methylcellulose can be applied as bulk purges, so some of its applications are to treat nose drops, burn preparations ointments, constipation, and in ophthalmic preparations. Using it as a bulk laxative which causes to absorb water completely regularly, tablets of methylcellulose cause intestinal obstruction and fecal impaction [27]. Constructing a bulkier and softer stool, therefore, it can treat the diverticulosis, constipation, irritable bowel syndrome, and hemorrhoids and also absorbs a huge amount of water into the colon. It should be taken with sufficient amounts of fluid to prevent dehydration. The common side effect is nausea and the less common side effects are vomiting and cramp [28]. On the other hand, solid dispersion in which compounds are dispersed into water-soluble carriers has been generally used to improve the dissolution properties and the bioavailability of drugs that are poorly soluble in water. Methylcellulose has the hydroxyl group in its structure and is interactive with the poly (ethylene oxide) (PEO) together with the carboxylic acid of a carboxyvinyl polymer (CP).

2.1.5 Microcrystalline Cellulose

Microcrystalline cellulose has many advantages in the formulation and production of solid dosage forms; however, it has some limitations such as sensitivity to lubricants, moderately low bulk density, loss of compatibility after wet granulation, and moderate flowability [29].

In order to improve the function of the microcrystalline cellulose, silicification is applied. Therefore, some properties such as compressibility, enhanced density,

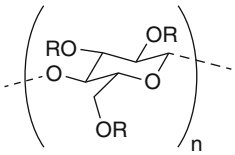

Fig. 5 Molecular structure of ethyl cellulose (R = H or CH_2CH_3)

compatibility, low moisture content, larger particle size, flowability, low moisture content, and lubricity will improve. By co-drying a suspension of colloidal silicon dioxide like dried finished product that contains 2% colloidal silicon dioxide and microcrystalline cellulose particles, silicified microcrystalline cellulose (SMCC) is manufactured. The silicon dioxide remains on the surface of microcrystalline cellulose. Rather than the usual kinds of microcrystalline cellulose, silicified microcrystalline cellulose displays higher bulk density [30].

2.1.6 Ethyl Cellulose

Ethyl cellulose is a natural polymer from cellulose derivative where the repeating glucose units are converted into ethyl ether groups (Fig. 5). This polymer is a pH-insensitive cellulose ether, nonionic and soluble in various polar organic solvents but insoluble in water. The functions of this polymer include insoluble factor in matrix or coating methods and a non-swellable polymer [31]. Ethyl cellulose is chosen whenever it is impossible to use water-soluble binders in dosage processing because of water sensitivity of the active ingredient.

To avoid the tablets from reacting with another material, this polymer can be applied to coat. To prevent discoloration of simply oxidize materials, for instance, ascorbic acid, and also combination with other polymers, is another application of this polymer. The combination of this polymer with water-soluble polymers is due to prepared sustained release film coating for the coating of tablets, micro-particles, and pellets [32].

2.1.7 Cellulose Ether

In designing the matrix tablets, cellulose ethers are extensively applied. Once they contact with water, the hydrogel layers start to propagate around the dry tablet's core, due to the cellulose ethers, and start to swell. The hydrogel offers a diffusional barrier for the molecules of water penetrating into the matrix of polymer and thus the molecules of the drug being released [33].

2.1.8 Hydroxypropyl Methylcellulose

Hydroxypropyl methylcellulose (HPMC) or hypromellose is a water-soluble derivative of cellulose ether and is able to apply as a hydrophilic polymer to prepare the controlled release tablets. The water penetrates to the matrix and hydrates the chains of polymer that ultimately separates from the polymer matrix. It is generally recognized that drug release from HPMC matrices follows two mechanisms, drug diffusion through the swelling gel layer and release by matrix erosion of the swollen layer [34]. Therefore, quantifying the percent contribution of diffusion and erosion to the overall drug release is important.

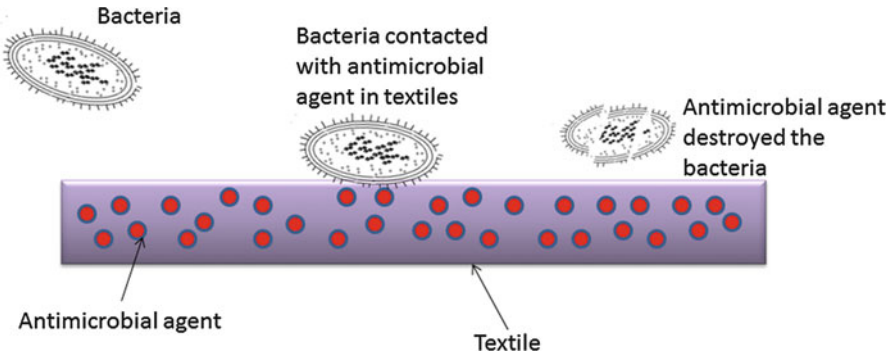

Fig. 6 Antimicrobial action of textiles incorporated with antimicrobial agents

Cellulose derivatives are often used to modify the release of drugs in tablet and capsule formulations and also as tablet binding, thickening, and rheology control agents, for film formation, water retention, and improving adhesive strength and for suspending and emulsifying [35].

2.2 Application of Antimicrobial in Textile Industry

Antimicrobial treatment is increasingly becoming a standard finish for some textile products such as for medical, institutional, and hygienic uses. Recently, it has become popular in sportswear, women's wear, and aesthetic clothing to impart anti-odor or biostatic properties [36]. Natural textiles such as those made from cellulose and protein fibers are often considered to be more vulnerable to microbial attack than man-made fibers in light of their hydrophilic porous structure and moisture transport characteristics. Thus, the use of antibacterial agents to prevent or retard the growth of bacteria as shown in Fig. 6 is becoming a standard finishing for textile goods [37].

2.3 Solid Dosage Form

Pharmaceutical scientists are increasingly using lipid-based excipients in the development of solid oral dosage forms for taste masking and as sustained release agents. The interest in this class of excipients is growing mainly since they can be applied in a variety of processes and since they are naturally occurring compounds that are predominantly digestible [38]. In dosage forms coated for the purposes of taste masking and immediate release, stability issues can lead to poor taste masking after storage, leading to patient dissatisfaction and poor adhesion to the therapy. A complex solid state of such dosage forms results from the structural hierarchy of the lipid-based excipients. Often, this complexity originates from the excipient's composition, in which triacylglycerols (TAGs) are combined with diacylglycerols, mono-acylglycerols, free fatty acids, phospholipids, or surfactants [39].

2.4 Tablets

The purpose of design and formulation of fast-release tablets is to make sure that a drug will be absorbed shortly, and also it is focused on fast achieving dissolution. The design and formulation of such tablets are to fully disintegrate within 2.5–10 minutes. Some of the applications of such tablets are to achieve appropriate bioavailability of a poorly soluble drug substance and/or for analgesics [40].

2.5 Superabsorbents for Personal Hygiene Products

In order to absorb fluids in personal care products, the selected hydrogel is acrylated-based superabsorbent hydrogels that are applying significantly. These products hold off the moisture from the surface of the skin that improves the comfort of consumer and health of the skin [41]. Some of the applications of this product include adult incontinence products and in training pants, in personal care stuff and their effectiveness and safety, preventing diaper rash and keeping skin dry and leakage prevention in diapers.

Harmon and Harper invented superabsorbent in 1966, but the application in the diaper industry was introduced in 1982 by Unicharm in Japan and afterward in sanitary napkins [42]. By using superabsorbent materials, high-performance diapers were invented that are thinner, and the diaper rash and leakage has reduced in them. The leakage values reduced to under 2% that shows a success in this product. This is an advantage in the environmental issues due to economic sense through reducing the cost of packaging.

Various efforts have been done to recycle napkins, hospital bed sheets, disposable diapers, and sanitary towels. The main purpose of recycling the diaper is to separate the cellulose that is recyclable and biodegradable [43]. The new generation of NaCMC-based hydrogels crosslinked with DVS has higher swelling capabilities rather than the SAP crosslinked hydrogels. They also have higher water retention under centrifugal loads. By using a phase inversion desiccation in acetone such as a non-solvent for cellulose, such important results will be achieved. This technique is based on a microporous structure that causes to increase the water absorption together with swelling kinetics using the capillary impacts. The most important benefit of cellulose-based hydrogels is their environmentally friendly and their biodegradability type [44].

2.6 Water Reservoirs in Agriculture

There is an increased value in using superabsorbent hydrogels to optimize the water resources and reduce the water consumption in horticulture and agriculture. This technique has novelty for the habits of culture and human toward the water. It is well known that during the swelling process in the hydrogels, the materials shift from glassy to plastic state that has water storing capability as shown in Fig. 7.

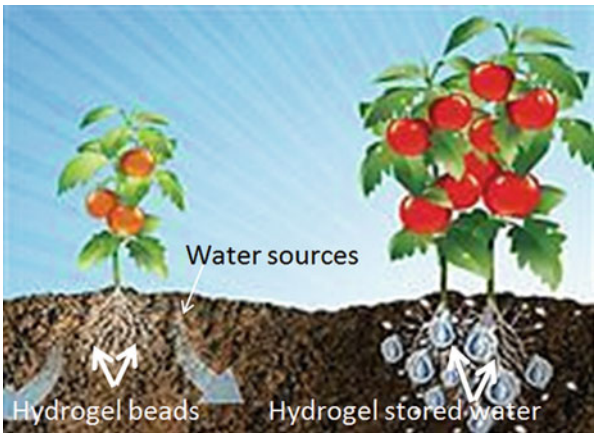

Fig. 7 Agricultural application of hydrogel for water storing purpose

Table 1 Water content in the soil as a function of the number of days after watering: effect of different hydrogel contents

	Hydrogel added into soil			
Measurement and observation	Control 0(%)	0.2 (%)	0.5(%)	1.0 (%)
Initial humidity in soil (%)	45	55	66	73
Plant survival time (days)	8	9	13	22
Water content at point of germination (%)	30	43	58	66

In this system, if a descent of humidity among the outside and inside of the material exists, then the swollen hydrogel can start to release the water through a diffusion-driven mechanism slowly [45]. During watering the cultivation, the water is absorbed by the dry hydrogels, and when needed the nutrients and water will be released from the hydrogels to the soil. As shown in Table 1, this method will cause to keep the soil humid for a long time.

Apart from water, other molecules that are loaded in the network of the polymer also can be released by means of diffusion in a sustained and controlled manner. The application of this procedure is to make the cultivation possible in desert and arid regions of the world. In this case, the dry hydrogel in the form of granules or powder will be mixed to the soil around the roots of the plant [46].

The dry hydrogel such as xerogel can be loaded with plant or nutrients pharmaceutical. The advantage of this procedure is to avoid the drainage and evaporation of water, soon after watering, and also can redistribute the water resources in another application. Another benefit of using hydrogels in this method is due to the impact of the swelling on the soil [47]. This positive impact is related to the size of the granules of the hydrogel in the soil before and after the watering. During the watering of the soil, the granules of the hydrogel absorb water and increase their dimensions; thus it will create porosity and pores in the soil which can improve the oxygenation of the roots of the plant. On the other hand, the size of the granules of such hydrogels in the soil is also very important. It is suggested that the large-granule hydrogels are better

than the small-granule ones [48]. If they mix properly with the soil, various dimensional shapes for the hydrogel particles and for the soil are possible, based on the interactions between hydrogel and soil hydrogel.

In the effort to develop environmentally friendly alternatives to acrylate-based super absorbent hydrogels, cellulose-based hydrogels prosper perfectly in a present manner. A novelty in the new generation of hydrogels is that they can absorb more than 1 l water for each gram of dry material with no release under the compression. The hydrogel is produced in the form of bulk material or powder material. The soil containing small quantities of the hydrogel can keep the humidity for long times rather than wet soil without hydrogel. This amount of keeping water is around four times more [49].

2.7 Body Water Retainers

The cellulose-based hydrogel has some specific properties that have the capability to appeal for in vivo applications. These properties include versatile and biocompatibility of cellulose. For instance, hydrogels hold potential as devices for the removal of extra water from the body, in the treatment of some pathological conditions, such as diuretic-resistant edemas and renal failure. It is predicted that the hydrogel in the powder form and orally administration absorbs water via its passage in the intestine and pH 6–7, but with no swelling in the acidic environment of the stomach. Because of the requirement to pH-sensitivity, polyelectrolyte cellulose hydrogels based on HEC and NaCMC have been considered for these applications. The hydrogels display enough swelling ratio at pH 7 and the low swelling ratio at acidic pH. The combination of hydrogel and drug for the intestinal pathway is beneficial to remove water from the body [50].

2.8 Stomach Bulking Agents

Superabsorbent hydrogels are interesting in stomach bulking due to not only their modulation through changing the conditions of the environment such as ionic strength, pH, and temperature but also their swelling capacity is designed by controlling the physical and chemical composition and microstructure. The hydrogels are administrated before each meal; this helps to reduce the free space for the food and giving a fullness feeling to the person. The hydrogel is envisaged to pass through the gastrointestinal tract, so it is supposed to confront the various pH of the intestine and stomach environments [51]. Accompanied by super porous acrylate-based hydrogels that swell fast in solutions, the novel cellulose-based hydrogels that are crosslinked by aqueous mixtures of HEC and NaCMC appeal for the production of dietary bulking agents.

These hydrogels have high pH-sensitive water retention capacity and high biocompatibility regarding intestinal tissues. The poly anionic network of NaCMC provides higher swelling potentials at neutral pH rather than acidic pH [52].

2.9 Devices for Controlled Drug Delivery

The cellulose ether on the surface of the tablet such as HPMC forms chain entanglements, starts to swell, and is a physical hydrogel. During the swelling process, the drug dissolves from the swollen surface to the glossy core of the tablet. The drug dissolves in water and diffuses from the network of polymer.

Some of the parameters such as mesh size, water content, and the degree of crosslinking can affect drug release. Dissolution of the chain happens with swelling, and it is related to the structure of the applied cellulose ether [53]. Therefore, drug release occurs from the erosion, complex combination of the swelling and erosion mechanism. The purpose of sophisticated hydrogel-based devices is not only at the sustained release of a bioactive molecule, ranging from hours to weeks, but also at a space-controlled delivery, directly at the site of attention. The reason to encapsulate the bioactive molecules into a hydrogel matrix such as microspheres is related to the short half-life presented by many biomolecules in vivo. During the applying hydrogels to moderate the drug release, the drug loading is achieved during network formation or crosslinking [54]. Additionally, to more modify the release rate, the bioactive molecule can be physically or covalently linked to the network of the polymer.

Smart hydrogels are applicable to control the space and time-release profile of the drug as deswelling-swelling transitions that tune the mesh size of the network of the hydrogel and occur via changes of physiologically relevant variables, for instance, temperature, pH, and ionic strength. Release from cellulose-based polyelectrolyte hydrogels is based on the strong pH variations. The latest advances in the controlled release are according to the protein delivery, gene-specific sites, and growth factors. However, to prevent more surgical removal and foreign body reactions, formulation of hydrogel for transdermal and oral delivery can be nondegradable; the direct protein or drug delivery to different parts of the body needs the biodegradation of hydrogels [55].

2.10 Scaffolds for Regenerative Medicine

Regenerative medicine is an interdisciplinary field that distributes with the stimulated regeneration of organs and tissues in vivo, with a scaffolding template or material that guide and support the cells during the synthesis of new tissues [56]. The high capacity of hydrogels in biocompatibility is due to their high-water content. This character makes them show some rubbery properties in similar condition with soft tissues and let the integration of bioactive molecules and cells during the gelling. Besides, although cells do not readily attach to highly hydrophilic surfaces, the surface or bulk chemistry of hydrogels can be easily modified with domains of the extracellular matrix that promote cell adhesion together with particular cell functions [57]. Consequently, hydrogels are ideal products to design the biomimetic scaffolds for tissue regeneration.

Cellulose and its derivatives have the high biocompatibility and good mechanical properties which is used as the design of tissue engineering scaffolds. Preferably, for finest tissue regeneration, the scaffold should be biodegradable, but practically a slow degradation is often preferred, in order to minimize the risks associated with an impulsive resorption of the scaffold. Despite its biodurability, cellulose is an ideal biomaterial candidate to the design of tissue engineering scaffolds [58]. On the other hand, a very slow degradation can cause unwanted responses such as body reaction in the long period that limits the cellulose applications.

Cellulose and its derivatives, usually in the form of fabrics or sponges, have been applied for the treatment of severe skin burns and in studies on the regeneration of bone tissues, cardiac, vascular, neural, and cartilage. With particular regard to cellulose-based hydrogels, a few independent investigations show that cellulose-based hydrogels are potentially beneficial for inducing the regeneration of neural tissues, bone, and cartilage. In a research, the pretreatment of a cellulose-based scaffold with cellulase before implantation has been planned, in an effort to modify the in vivo degradation cellulose behavior. The benefit of using cellulose rather than other natural or synthetic polymers for tissue engineering purposes is due to the final product of cellulose degradation that is glucose and is a nutrient for cells. Cellulose-based hydrogels are valuable throughout cellulose fabrics and sponges because their bulk chemistry can be easily modified. The biocompatibility of the crosslinking agent used is particularly important, especially in cases where reactive groups of the crosslinker are incorporated into the hydrogel network and might then be released upon degradation.

Hydrogels based on HEC, NaCMC, and (hyaluronic acid) HA have been recently crosslinked with a water-soluble carbodiimide, which is both "zero-length" and nontoxic crosslinker. The carbodiimide, which is washed out from the polymer network after the synthesis, is well-known to induce the formation of ester bonds among polysaccharide molecules without taking part in the linkage [59]. It is worth noting that the ester bonds forming the network have the potential to be digested, in the long term, via hydrolysis, as it normally occurs for synthetic polyesters. Thus, cellulose-based hydrogels crosslinked with carbodiimide show potential for a tunable biodegradation rate, even when not containing HA. Although an investigation on the biodegradation behavior of such hydrogels has not been performed yet, it is reasonable to hypothesize that the degradation rate can be modulated to some extent by controlling the degree of crosslinking.

The mechanical stiffness of the hydrogel is also dependent on the degree of crosslinking and should be designed according to the tissues being addressed. Furthermore, the carbodiimide-mediated crosslinking reaction holds promise for the functionalization of cellulose with several biomolecules, able to promote specific cell functions, due to the ability of the carbodiimide to crosslink various polypeptides. This opens a wide range of possibilities for the design of biomimetic, cellulose-based hydrogel scaffolds for tissue engineering [60].

A final remark regarding the development of regenerative templates concerns the key role played by the scaffold porosity, which enhances the attachment, infiltration, and survival of cells within the scaffold. Due to their nano-sized mesh structure,

Fig. 8 Bacterial cellulose for wound dressing

hydrogels are usually employed to treat small tissue defects while failing in larger implants. Novel manufacturing techniques aiming at the development of several types of porous hydrogels are being investigated and might be of great value in enhancing the regenerative potential of cellulose-based hydrogels as well.

2.11 Wound Dressings

Some process is occurring during the wound healing such as reepithelialization, autolytic debridement, granulation tissue formation, and inflammation. A proper wound dressing is to support healing of the wound from infection. Hydrogels are ideal candidates to develop the wound dressing, as an amorphous or a sheet because the moist in the environment makes the healing fast. The viscosity of amorphous hydrogels during the absorption of fluids decreases due to their physical crosslinking [61]. Hydrogel transparency is an additional advantage as wound healing can be undoubtedly observed. The hydrogels including silver ions in their structures are the most advanced hydrogel dressings.

Figure 8 shows bacterial cellulose (BC) which has been extensively examined for wound healing due to its high-water retention capacity and its purity. NaCMC as gel-forming cellulose derivatives is embraced in the formulation of some hydrogel dressing. Regarding this matter, usually, propylene glycol is in combination with NaCMC that works as a preservative and humectant [62].

3 Swelling Controlled Release Systems

Generally, a swelling-controlled release system of a hydrogel shows the swelling ratio increases with time up to 16 h and then continues to increase with time but at a lower rate.

This phenomenon can be explained by the chemical potential difference:

$$\mu_1 - \mu_{1.0} = \Delta\mu_{\text{mixing}} + \Delta\mu_{\text{ionic}} + \Delta\mu_{\text{elastic}}$$

Here, $\mu_1 - \mu_{1.0}$ is the chemical potential difference between solvent and polymer; $\Delta\mu_{\text{mixing}}$ is the chemical potential difference, defined as interactions between polymer and solvent; $\Delta\mu_{\text{ionic}}$ is the ionic chemical potential difference; and $\Delta\mu_{\text{elastic}}$ is the chemical potential difference for elastic, always acting against the swelling. Both $\Delta\mu_{\text{ionic}}$ and $\Delta\mu_{\text{mixing}}$ facilitate the swelling process. At the beginning of the swelling process, $\Delta\mu_{\text{ionic}}$ controls the swelling, but after equilibrating between hydrogel internal and external ions, $\Delta\mu_{\text{mixing}}$ dominates the swelling process with a value less than $\Delta\mu_{\text{ionic}}$. As a result, the swelling trend initially increased and then decreased [33, 63]. Figure 9 shows an example

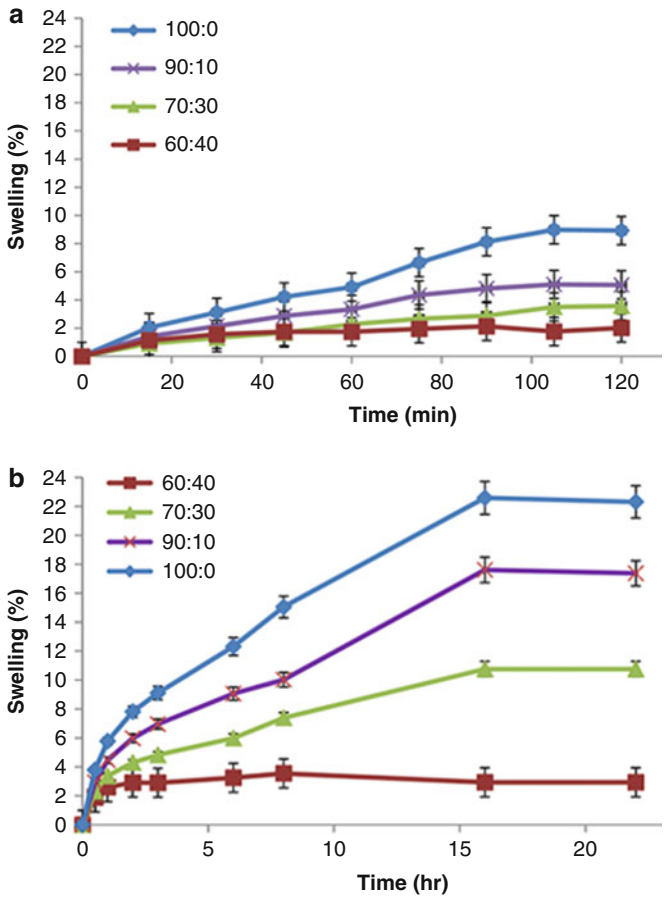

Fig. 9 Swelling of kappa-carrageenan/hydrohyethyl cellulose hydrogels of different concentration in (**a**) pH 1.2 and (**b**) pH 12 at room temperature

of observation among almost all of the blend ratios where after 2 h in acidic medium, the kappa-carrageenan/HEC hydrogels reached equilibrium.

The protonation of carboxylic groups and the creation of more hydrogen bonds in κC hydroxyl groups results in more compact networks and hence less swelling. Most blend ratios showed more swelling in an alkaline environment than acidic. This phenomenon can be due to electrostatic repulsion of polymer chains as a result of ionization of carboxylic acid groups that breaks the hydrogen bonds. The repulsion force will then push the hydrogel network to expand; thus more water can enter into the network [63].

Esterification of NaCMC with acryloyl chloride also was reported to improve the swelling properties such as the degree of swelling of the esterified product changes as the pH was varied [64]. At pH 9.4 the swelling percentage was quite high compared to that at pH 1.2, so it can be used as a pH-responsive polymer for the various biomedical applications. Since this polymer swells at high pH and collapses at low pH values, this polymer can be used in oral delivery, in which the polymer will retard drug release at low pH values in the stomach while releasing the same at high pH values in the small intestine. Hence this polymer can be used for pH-sensitive drug delivery system like aspirin, indomethacin, diclofenac, etc. in the intestine and also as a wound dressing material [65].

4 Conclusion

Cellulose-based hydrogels are biodegradable and biocompatible materials that indicate promise for a number of industrial uses, particularly in cases where environmental issues are concerned, aside from biomedical applications. Most of the water-soluble cellulose derivatives can be applied, with blending or singularly to make the networks of hydrogel including particular characteristics for the sensitivity to external stimuli and swelling capability. This manner of designing the cellulose hydrogels is for the nontoxic crosslinker agents of the hydrogels or crosslinking treatments in order to increase the safety of manufacturing process and the final product. Some of the cellulose derivatives such as HPMC and NaCMC show smart behavior to physiological variables such as temperature, pH, and ionic strength that make the hydrogels suitable for in vivo applications. Despite the non-bioresorbability of cellulose, the possibility to functionalize cellulose-based hydrogels with biodegradable extracellular matrix domains and bioactive indicates that such hydrogels might be ultimate platforms for the design of scaffolding biomaterials in the field of regenerative medicine and tissue engineering.

5 Future Prospects

Absorbent hydrogels are good candidates for captivating neutral aqueous solutions which are characterized by two main features, equilibrium swelling and swelling rate. Generally, two methods have been practiced to improve the swelling rate of

hydrogels: (a) size reduction of the hydrogels and (b) introduction of superporosity into the hydrogels structure. Although synthetic electrolyte and nonelectrolyte hydrogels are being used in a variety of applications, research is moving toward more biocompatible and environment-friendly natural polymer alternatives, such as those based on cellulose.

During the past several decades, cellulose-based hydrogels have already exerted a dramatic impact in biological, biomedical, pharmaceutical, and diagnostic fields. However, there are some intrinsic shortcomings that severely restrict their potential practical applications. Significant efforts have been paid to improve the performance of the cellulose-based hydrogels. The fabrication of cellulosic composite materials by combining two or more components in a single entity can surmount individual shortcomings and give rise to synergistic functions that are absent in the individual components. The incorporation of nanoparticles in three-dimensional cellulosic hydrogel matrix as an innovative means to obtain cellulosic nanocomposite hydrogels with improved properties and multiple functionalities has gained enormous attention in many areas.

Due to their unique swelling features, superabsorbent cellulosic hydrogels could be employed as intelligent materials where the absorbent is required to perform numerous cycles of absorption and desorption. Cellulose-based porous hydrogels as well as thermo-responsive hydrogels have found very specific applications, where properties other than swelling capacity and rate are required. Self-assembled or self-organized hydrogels as well as those based on natural polymers could influence more advanced applications of cellulosic hydrogels.

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Cellulose-Based Hydrogel for Industrial Applications

29

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Abstract

Cellulose-based superabsorbent hydrogels can absorb and retain huge amounts of water or aqueous solutions. They have a wide range of industrial applications including (a) hygienic and bio-related uses (more specifically in disposable diapers); (b) agricultural uses (such as water reserving in soil, soil conditioning, and controlled release of agrochemicals); (c) pharmaceutical dosage forms; (d) separation technology; (e) textile, leather, and paper industries (such as in wastewater treatment); (f) water-swelling rubbers; (g) soft actuators/valves; (h) electrical applications; (i) construction, packaging, and artificial snow; (j) sludge/coal dewatering; and (k) fire extinguishing gels. Many new advanced technologies are evolving by the day to cope with rigorous industrial-scale applications to ensure improved technical feasibilities. This chapter will briefly cover some of the selected aspects of cellulose-based hydrogels and their industrial applications.

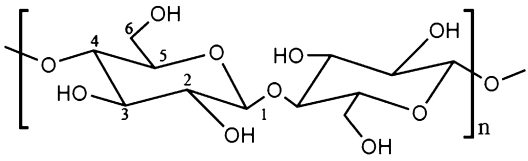
Keywords

Cellulose · Hydrogels · Superabsorbent hydrogels · Composite · Stimuli-responsive hydrogels · Carboxymethylcellulose

1 Introduction

Hydrogels have three-dimensional structure with elastic network that can span the volume in aqueous media. Hydrogels can be both natural and man-made [1–10]. Natural hydrogels are important components of different complex organisms that include (a) the bodies of jellyfish, (b) connective tissues in joints, (c) cornea in the eye, and (d) nuclear pore complexes inside cells. Synthetic or man-made hydrogels have a wide range of applications in different areas of life sciences including biomedical applications, where some of the important uses are (i) contact lenses, (ii) drug delivery, and (iii) tissue engineering [2–16]. Hydrogels are mostly polymer-based, and their networks usually contain covalently cross-linked natural or synthetic polymers, whereas the supramolecular hydrogels use nanofibers to form the

Scheme 1 Molecular structure of cellulose



self-assembly of small molecules (such as hydrogelators), which have many promising applications [1–16]. In this context, natural polymers such as cellulose are very popular and frequently used for a variety of applications in hydrogel formulations apart from their numerous other uses in different areas of science and technology. One of the many practical aspects of the use of cellulose in hydrogel formulations is its abundant availability (as a natural biomaterial) in the form of a living terrestrial biomass suitable for a wide range of industrial applications [16–27].

Cellulose molecules have three alcoholic hydroxyl groups in each of its anhydroglucopyranose units where practical chemical modifications can be carried out on these hydroxyl groups of cellulose structure (Scheme 1). At first in 1838, the existence of cellulose as the common material of plant cell walls was recognized [17, 18]. It has a long-chain polymer with repeating units of D-glucose (like a simple sugar). For example, this repeating unit occurs in almost pure form in cotton fiber, whereas in wood, plant leaves, and stalks, it is found in combination with other materials (for instance, lignin and hemicelluloses). In addition, some bacteria also produce cellulose. Natural cellulosic polymer has a long chain which links smaller units (such as β-D-glucose-type sugar unit) in the cellulose chain [19], and the sugar units are linked by the elimination of a water molecule. In addition, when two of these sugars are linked, it produces a disaccharide called cellobiose [20]; however, it gives pyranoses (with six-membered rings) when this chain contains the glucose units. In addition, cellulose is a linear chain of anhydro-D-glucopyranose (AGU) units in a chair conformation with hydroxyl groups in equatorial positions, and every other AGU is rotated to preserve the thermodynamically favored acetal bond angle of the β-1,4-glucosidic bonds [21, 22]. In the plant cell wall, the cellulose chains have a degree of polymerization of 2,000–15,000 AGUs, depending on the type of plant and cell wall (primary or secondary) [23]. A single cellulose chain usually passes through both crystalline and amorphous regions and in crystalline regions; 30–36 cellulose chains associate laterally through hydrogen bonding [24]. The extensive, regular hydrogen bonding of the cellulose chains contributes to make the crystal impermeable and increases the difficulty of extracting and degrading the cellulose [25]. Additionally, elementary cellulose fibers have diameters of around 5 nm, and several of these elementary fibers will bundle together with hemicelluloses to form cellulose microfibers with diameters of 10–30 nm and lengths of around 7 μm [21, 26]. These cellulose microfibrils form an open matrix in the cell wall, and the pores of these microfibrils are filled with hemicelluloses and pectin (primary cell wall) or lignin (secondary cell wall) [27]. In this chapter, different aspects of certain types of cellulose-based hydrogels are briefly presented, and these selected groups are (a) cellulose- and cellulose derivative-based hydrogels, (b) cellulose

composite- and cellulose nanocomposite-based hydrogel systems, (c) functionalized cellulose-based hydrogels, and (d) hybrid cellulose-based hydrogels.

2 Cellulose-Based Hydrogels

Nature is the main source of cellulose. It is a carbohydrate-type natural polymer, and it also has other attractive properties which include (a) biocompatibility, (b) biodegradability, (c) environmentally benign, and (d) cheap and renewable. In addition, cellulose contains hydroxyl groups in its structure that provide a unique suitability to produce superabsorbent hydrogels with attractive structures and desired characters. Since the advent of superabsorbent polymers in 1950, notable progress has been achieved within the last few decades in the field of superabsorbent hydrogels. One of the main driving forces behind this is the main concern of continuously increasing customer demands for high-quality superabsorbent materials for industrial applications primarily in the sanitary industry. Superabsorbent hydrogels have hydrophilic networks that provide higher capacity in water uptake and facilitate the capacity for water absorption and swelling. A good quality superabsorbent hydrogel can retain aqueous solutions up to hundreds of times compared to the weight of dry hydrogel [1–3]. Usually superabsorbent hydrogels are produced from synthetic polymers; however, there is a current trend to replace these polymers using environmentally benign and sustainable green alternatives such as natural polymers like cellulose and their products [4]. Cellulose-based superabsorbent hydrogels have been successful to attract current active research interest due to their many practical and potential industrial applications. For example, when celluloses or their derivatives are used in the synthesis of superabsorbent hydrogels, they provide the opportunity to overcome different demerits associated with synthetic-based superabsorbent hydrogels and also contribute to meet many requirements relating to environmental issues and other desired set criteria for specific applications [5]. In addition, it is possible to add multifunctional character on hydrogels by incorporating functional molecules into the structure of the hydrogels. Additionally, cellulose-based superabsorbent hydrogels typically show higher properties in comparison to properties observed from synthetic superabsorbent hydrogels; these properties include (a) absorbency, (b) strength, (c) biodegradation capability, (d) biocompatibility, and (e) good salt resistance [28–39].

2.1 The Emergence of Hydrogels as Biomaterials

Hydrogels are one of the few ever-evolving biomaterials which have been rigorously studied due to their wide range of application potentials in different areas of science and technologies including biomedical, therapeutic, and diagnostic application purposes. Hydrogels provide many unique feasibilities to incorporate vivid range of materials (such as biopolymers, synthetic polymers, nanoparticles, hybrid materials, composites, and nanocomposites) to form their tailor-oriented suitable structural

morphologies using different techniques in order to serve specific desired uses. Besides these wider advantages, there are also some factors (such as proper and stable dispersion of hydrogels and nanoparticulate systems) that limit their uses in different areas. From a comprehensive study on the recent development trends on different hydrogel systems, it is quite transparent to observe that the incorporation of nanostructured fillers into hydrogels has been systematically enhanced using novel techniques to synthesize novel hydrogels that can successfully retain different functionalities to address different challenges. This chapter concentrates on the applications of carboxymethylcellulose (CMC)-based hydrogels along with other related hydrogel systems such as CMC-based composite, nanocomposite, hybrid, and functional hydrogel systems and their general method of fabrications as well as their applications. In addition, it also shed some light on the fundamentals of hydrogels and nanoparticles (NPs) along with recent advances in the field of design, synthesis, functionalization, and application of nanocomposite hydrogels with improved characters (such as mechanical, biological, and physicochemical behaviors). Besides this, it also briefly states the current challenges and future opportunities for the successful applications of hydrogels (including composite- and nanocomposite-based hydrogel systems) in particular areas (such as industrial applications of cellulose-based superabsorbent hydrogels) [35, 37, 38, 40–65].

3 Cellulose Composite-Based Hydrogels

Cellulose, the most abundant natural biomass, possesses very promising properties, some of which include mechanical robustness, hydrophilicity, biocompatibility, and biodegradability. Cellulose-based composites have many applications, for example, in drug delivery systems, hydrogels, electronic active papers, sensors, shape memory materials, and smart membranes. It also offers interesting potential improved properties and new functionalities when used in hydrogel formulations using appropriate methods. For example, cellulose-based stimuli-responsive smart materials can be used for hydrogel synthesis, and the hydrogels produced from these materials have many advantages, some of the most important ones include regulation of stimuli-responsive behaviors during the reactions with the environmental stimuli and wide application potentials of these smart materials in different fields (for instance, as biomaterials). Different methods can be used to incorporate different stimuli- responsive materials into the structures of cellulose composites in order to regulate different properties of the bulk composite structures which can be tailored to make them suitable properties for their use in composite-based hydrogel systems [66–132]. Environmentally stimuli-responsive cellulose composite-based hydrogels have many conventional and high-tech applications, but there are quite a lot of challenges in order to produce high-quality stimuli-responsive cellulose composite-based hydrogels that meet desired criteria and mitigate challenges. This chapter discusses different selective aspects of environmentally stimuli-responsive cellulose composites and their uses in hydrogel productions and their potential industrial applications.

3.1 Cellulose-Based Stimuli-Responsive Hydrogels

The abundance of hydrophilic groups on the chains and slightly cross-linked structure hydrogels allows them to absorb large amounts of water which they can release at dry conditions. Hydrogels are also widely used in food, biomaterials, agriculture, and other industrial applications [6, 10, 133–247]. The syntheses and uses of hydrogels based on cellulose have been reviewed by other researchers [6, 10, 247], so some selective studies on stimuli-responsive hydrogels based on cellulose are briefly discussed. The superabsorbent nanocomposites based on CMC and rectorite also exhibited saline, pH, and organic solvent-responsive behaviors. Stimuli-responsive smart hydrogels based on cellulose nanocrystals contributed to improve the swell capacity and the mechanical strength of the hydrogels [133, 224]. Based on titanium dioxide-based coated, native nanocellulose aerogel networks, a novel photo-controlled switching between the water superabsorbent and water-repellent states has been reported [204]. In the stable state, titanium dioxide-based coated aerogels did not show any water absorption; however, the original absorption and wetting properties slowly recovered when stored in the dark. Besides this photo-induced absorption and wetting behavior, titanium oxide coated nanocellulose aerogels also exhibited photocatalytic activity and capability to decompose an organic material (such as methylene blue). Electrospinning or coating techniques have been used to prepare pH-responsive hydrogel fibers from cellulose which have potential applications in the fields of cotton knitwear and biomaterials [134, 156].

3.2 Applications of Environmental Stimuli-Responsive Cellulose Composites in Combination with Cellulose-Based Hydrogels

Cellulose-based biocomposites and nanocomposites have a very wide range of potential applications. For example, nanocellulose-based materials are extensively used in various applications including in the manufacture of paper and packaging products as well as in construction, automotive, furniture, electronics, pharmaceuticals, cosmetics, and biomedical applications. Additionally, they have very useful properties (e.g., the higher strength and stiffness, the higher surface reactivity due to the presence of numerous hydroxyl groups, the specific organization of the small dimensions of nanocellulose) suitable for reinforcement with nanofibers to enhance desired mechanical and physical properties for high-tech applications. Cellulose-based hydrogels can be used for coating and pretreatment on cellulose composite product for their various applications in different areas including (a) pharmaceutical products and packing, (b) specific high-quality papers for electronic and sensoric applications, (c) cellulose-based diagnostic chips for biomedical applications, and (d) cellulose-based specialty product for high-quality printing and packaging. Additionally, cellulose-based hydrogels produced from stimuli-responsive cellulose-based nanocomposites (responsive to pH, temperature, redox potential, light, magnetic field, and electrical field) have many potential applications in drug delivery systems, some of which include (a) promotion in controlled drug release and (b) controlled delivery

in specific intracellular locations or to targeted tissues. Stimuli-responsive smart drug delivery systems have been intensively investigated and reviewed in recent years [237–245]. Additionally, when hydrogels produced from cellulose-based nanocomposites with capability to show responsive behaviors have unique properties, for example, (a) biocompatibility, (b) biodegradability, and (c) biological functions. This type of products has been successful to draw the attentions of many researchers all around the world to explore these materials for practical industrial-scale exploitations because of their attractive uses including drug delivery systems, tissue engineering, and related biomedical applications. For example, stimuli-induced self-assembly and post-assembly triggering strategies can be used as an alternative approach to manipulate self-assembled architectures of synthetic polymeric aggregates in drug delivery systems. The assembly of polymeric aggregates contributes to transmit and change hydrodynamic radius changes, so drugs loaded in the assembled polymeric aggregates can be used for a controlled release when they disassemble after they are exposed to particular environmental stimuli (such as temperature and pH). For example, Sui et al. studied the temperature- and pH-sensitive characteristic of cellulose-*g*-PDMAEMA by using UV detection and dynamic light scattering technique [158]. The lower critical solution temperature (LCST) of aqueous cellulose-*g*-PDMAEMA solution was measured to be 42 °C, and when the thermal environment was below this temperature, the solution was transparent, and the value of hydrodynamic radius increased slightly with temperature increase (25–40 °C). On the contrary, when the temperature was raised to the range of 42–55 °C, the solution became opaque, and the value of hydrodynamic radius increased abruptly. At a low temperature in the surrounding environment, the cellulose-*g*-PDMAEMA copolymer chains exhibited random coil conformation because of the hydrogen-bonding interactions between the copolymer and water molecules. However, when the temperature was raised to LCST, polymer chains showed a shrinking into a globular structure due to the hydrophobic interactions between *N*,*N*-dimethylaminoethyl groups. In addition, the cellulose-*g*-PDMAEMA was dissolved in aqueous hydrochloric acid (with pH 2.0 at room temperature) and was precipitated in an aqueous alkaline condition (pH 12.0). Moreover, at lower acidic pH, due to the geometrical constraint and the electrostatic repulsion between polymer chains, the PDMAEMA chains were entirely protonated and highly stretched along the radial direction. Yuan et al. reported the synthesis of amphiphilic ethyl cellulose brush polymers with mono and dual side chains, which showed promising properties with dual temperature and pH response [154].

Stimuli-responsive cellulose-based hydrogels or similar types of other hydrogel-based products with the capability to exhibit swelling or shrinking when exposed to external stimuli (such as pH, temperature, light, magnetic field, etc.) have many potential biomedical applications because of their unique characteristic properties (e.g., biocompatibility, biodegradability, and biological functionality) [10, 247]. The swelling and shrinking mechanism of hydrogels is similar to that of aggregate assembly usually observed during stimulus-induced intermolecular and intramolecular hydrogen-bonding changes. Targeted drugs can be released controllably from drug-loaded hydrogel carriers when hydrogels swell to more loose structures when

exposed to environmental stimuli (with a proper control on this stimulus). Similarly, redox-responsive hydrogels have many application potentials for controlled drug release [150]. In addition, stimuli-responsive cellulose-based hydrogels incorporated with functional microcapsules and nanoparticles materials have many practical application potentials in pharmaceutical industry. For example, magnetic-responsive systems are widely used to trigger drug release at target sites and can also be applied to concentrate the drug-specific-responsive carriers. Magnetic cores encapsulated with ethyl cellulose have the potential to improve the biocompatibility and 5-fluorouracil loaded in the nanoparticles for a controlled release on specific sites during treatment of cancer [236]. Magnetic particles coated with hydroxy propyl cellulose exhibited response to thermal and magnetic environments which have many potentials for nanomedical applications (e.g., remote-controlled drug carriers) [174]. This type of products has been investigated to functionalize hydrogels for advanced life science applications. Lastly, controllable pore size of stimuli-responsive membranes is highly used in drug delivery. For example, cellulose-based membranes produced by incorporating stimuli-responsive materials can change their pore size according to the environmental conditions [6, 155]. So, drug delivery systems based on smart stimuli-responsive membranes can be used for a controllable drug release by an effective control on the stimulus that control the nature of diffusion through the membranes. For example, when CMC ethers mixed with aspirin were pressed to the tablet membrane, they showed zero-order release of the drug based on pH-responsive properties. This reversible glucose responsiveness was attributed to the reversibility of swelling and shrinking of the nanoparticles in response to changes of pH [199]. They can also be used in cellulose-based stimuli-responsive hydrogel fabrications. Cellulose derivative-based membranes embedded with liquid crystal molecules also showed temperature-responsive drug permeation characteristics [183, 184]. Suedee et al. prepared an MIP incorporated cellulose membrane for enantioselective-controlled delivery of racemic drugs with pH-responsive characters where (*S*)-omeprazole was used as an imprinting molecule conferring stereoselectivity upon the polymers [185]. Cellulose-based superabsorbent hydrogels have the potentials to be incorporated with this type of advanced systems to offer higher functionality suitable for high-tech applications in different areas of biomedical and life sciences [6, 10, 133–140, 143–152, 156–170, 174–190, 193–201, 205, 206, 210–225, 230–247, 253–264]. Generally, different environmental stimuli (such as light, temperature, pH, and ionic strength) can be used as triggers for the formation of supramolecular hydrogels. Additionally, inherent biological processes can be used to synthesize supramolecular hydrogels that are useful for biomedical applications. Biomimicking biomacromolecular self-assembly (e.g., formation of collagen fibrils, the integration of enzymatic reactions with self-assembly of small molecules) is an important technique for formation of nanofiber networks that can be used to produce hydrogels under various conditions. Enzymatic reaction can be used to initiate the self-assembly of a derivative of Taxol in aqueous solution to form nanofibers for producing supramolecular hydrogel. Cellulose derivatives can also be used for producing composite-type biomimetic hydrogels [253–270].

4 Cellulose-Based Functional Hydrogels

Composite hydrogels are produced using a variety of ways where some principle techniques include the incorporation of a range of suitable compatible materials into hydrogel structure or the assembly of hydrogels with other suitable structures (such as electrospun nanofibers) for serving specific purposes. This type of composite hydrogels can be used in various uses in everyday life (e.g., superabsorbers, contact lenses, drug delivery) [3–11, 129–181]. This type of composite hydrogels can be further functionalized by incorporating additional functionalities to produce functionalized hydrogels for many conventional and high-tech applications. For example, some particular type of hydrogels can be easily functionalized by introducing responsive characters which can respond to external stimuli. Some cross-linked polymers are responsive to various stimuli including light, temperature, pH, pressure, chemical (certain), electrical field, magnetic field, enzyme, and biological agent. By the careful and controlled use of responsive characters of the hydrogels produced by using these responsive polymers, they (hydrogels) can be applied in many fields like drug delivery, tissue engineering, and purification and implementation as actuators and biosensors or for medical coatings. In addition, cellulose can be used in combination with other suitable polymers to produce composites which can be used for hydrogel preparations [6, 10, 133–140, 193–201, 205, 206, 210–225, 230–247, 253–264].

4.1 CMC-Based Analyte-Sensitive Hydrogels

Carboxymethylcellulose (CMC) and their derivatives have the potentials for producing analyte-sensitive hydrogels that incorporate optical structures, and this type of hydrogels is particularly attractive for many emerging applications including their uses as sensing platforms for point-of-care diagnostics. In this case, the optical properties of the hydrogel sensors need to be rationally designed and fabricated using different techniques including (a) self-assembly, (b) microfabrication, and (c) laser writing. Main merits of CMC-based or similar other polymer-based photonic hydrogel sensors over the typically used conventional assay formats include (a) reusability, (b) free from labeling, and (c) quantitative as well as continuous measurement capability with potential for integration to equipment-free text or image display applications [253–264]. Here in this section of this chapter, we briefly explain different aspects of photonic hydrogels and their applications as sensors; we also present different important ways for the syntheses of CMC and other celluloses or polymers as well as quantum dot-doped composite hydrogel systems and their industrial applications. When photonic structures (such as quantum dots or functional molecules that can be modulated for photonic uses) are incorporated into CMC, cellulose, or other polymer-based hydrogel structures, this embedding or introduction causes certain level of change that contributes to alter the water contents and volumes of hydrogels and also changes the level of interactions with specific analyses. This

phenomenon offers a potential new platform to fabricate different biomedical diagnostic devices (such as IVD devices). In general consideration, hydrogels are 3D polymer networks that can be used for variable volume changes by controlling the variations of Donnan osmotic pressures applied on the hydrogel systems [254, 255]. By careful design to incorporate different suitable materials (such as quantum dot and responsive polymers) into hydrogel structures, sensitive hydrogels can be prepared that will be responsive to a range of stimuli as well as clinically relevant analytes [255, 256]. When functional molecules (such as bioactive recognition molecules and stimuli-responsive polymers) are incorporated into hydrogels to provide bioactive functional properties, the produced hydrogels show responsive characters on exposure to external stimuli by changing their physical and chemical characters to certain extent [255, 257]. For example, functional materials like quantum dot-doped hydrogels are useful for the fabrication of optical signal transduction and reporting within one device. Different reports that deal with bottom-up or top-down nano-/microfabrication methods are available that studied the feasibility of fabrication techniques for the miniaturization and multiplexing hydrogel-based photonic structures [258–265]. By the interaction of a target analyte and modulating reflection, diffraction, refraction, surface plasmon resonance, or emission [266] characteristics, the volumetric change in the hydrogel structure can be monitored, and the change in optical properties can be used to work as transducers that provide the opportunity for spectroscopic analysis (such as the concentration of the analyte, when this type of hydrogels are used for quantitative analysis). Besides this, CMC- or similar other polymer-based photonic hydrogels have the potentials to be used as sensors for tuning and reporting visually distinguishable color changes with a scope for semiquantitative determination without the use of an equipment. CMC- or their derivative-based photonic hydrogel sensors can be used for different biomedical applications. These photonic hydrogels may also have optically active elements with capabilities in displaying 3D images or writing [267–269]. Hence, the development of photonic hydrogel sensors has immense potential for both equipment-free semiquantitative diagnostics and quantitative analyzers that are compatible with mobile spectrophotometers and smartphone readers [270–278]. The potential applications of photonic hydrogel sensors are not limited to medical diagnostics but also include veterinary testing, pharmaceutical bioassays, and biohazard and environmental monitoring. However, the main focus area of hydrogel sensors has been in the detection and/or quantification of chemicals and cells in medical diagnostics. For example, their potential applications in biochemistry and biology are monitoring enzyme activity and metabolites [279] and serum albumin ligand binding [280–282]. Another potential area of application of photonic hydrogel sensors includes the detection of biocontaminants, heavy metals, and nanoparticles in water or air. The development of environmental sensors is aligned with the strict regulations imposed by the European Union and the United States. Reusable hydrogel-based sensing of environmental contaminants is an emerging area that can significantly reduce the costs and turnaround time at resource-limited settings.

4.2 Quantum Dot (QD)-Doped Cellulose-Based Hydrogels

Quantum dots are often used for the functionalization of hydrogels including cellulose-based hydrogels. For example, Baruah et al. reported the synthesis of functionalized graphene oxide quantum dots (GOQDs)-poly(vinyl alcohol) (PVA) hybrid hydrogels by using a simple, facile, and cost-effective strategy [283]. They introduced GOQDs bearing different surface functional groups as the cross-linking agent into the PVA matrix for gelation. They synthesized four different types of hybrid hydrogels by using graphene oxide, reduced graphene oxide, ester functionalized graphene oxide, and amine functionalized GOQDs as cross-linking agents. They found that the hybrid hydrogel prepared with amine functionalized GOQDs exhibited the highest stability compared to other hydrogels prepared by using other cross-linking agents. They used this stable hydrogel to explore the feasibility for an easy, simple, effective, and sensitive method for optical detection of M^{2+} (Fe^{2+}, Co^{2+}, and Cu^{2+}) in aqueous media involving colorimetric detection. They observed that when the amine functionalized GOQD-PVA hybrid hydrogel was exposed to the corresponding solution of Fe^{2+}, Co^{2+}, and Cu^{2+}, it showed, respectively, brown, orange, and blue color changes of the solutions and contributed to detect the presence of Fe^{2+}, Co^{2+}, and Cu^{2+} ions in the solutions. They also noted that this system can also be applied for sensing a mixture of coexisting ions in solution. It is possible that this piece of work can be extended to produce cellulose- and PVA-based composite systems for hydrogel formulations for detecting metal ions from solutions. El-Salmawi synthesized polyvinyl alcohol (PVA) and carboxymethyl cellulose (CMC)-based hydrogel using three different techniques (freezing and thawing, electron beam irradiation or combined freezing and thawing, and electron beam irradiation) and then applied the hydrogel for particular applications [284]. Then she carried out a comparative study between the three techniques in terms of gel fraction (%) and swelling (%). She observed that the physical properties of the hydrogel showed improved results when the combination of freezing and thawing and irradiation was applied rather than just freezing and thawing or irradiation only. She examined the effects of temperature and soil fertilizers on swelling (%) in order to evaluate the usefulness of the hydrogel as a superabsorbent material for its applications in the soil. She also observed that the swelling ratio increased as the composition of CMC increased in the blend. During the study, she used the blend having the composition 80/20 (CMC/PVA) and examined its behaviors as a superabsorbent in the soil for agricultural applications. She also noticed that the water retention increased in the soil containing this hydrogel. Thus, this type of hydrogel can be used to increase water retention in desert regions [284].

4.3 Cellulose Nanocrystal (CNC)-Based Hydrogels

Cellulose-based nanocrystals are also used for the formulation of different types of hydrogels due to many advantages that include (a) low cost, (b) biocompatibility, (c) biodegradability, and (d) good mechanical properties and chemically reactive

surfaces. In addition, cellulose nanocrystals are a promising class of nanomaterials that have a wide range of application potentials for a variety of industrial uses. Some of the main industrial uses include (a) food packaging, (b) personal care, (c) biomedical devices, (d) textiles, (e) separation technologies, (f) construction materials, and (g) paper and similar paper-based product industries [1–11, 33–73, 131–152, 156–170, 171–180, 195–200, 205–224, 240–264]. Cellulose nanocrystals have some significantly important characters (such as large aspect ratio, high strength, and lightweight) and also have the required capability to be chemical cross-linked in order to modify that chemical and physical properties. All these attractive features make cellulose nanocrystals attractive for their use in hydrogel formulations using different strategies including the injection of these materials into the structure of hydrogels and aerogels to produce desired technical characters (such as robust mechanical properties). Thus, it is a popular trend to use chemically cross-linkable cellulose nanocrystals as nanofillers to reinforce injectable hydrogels and also to use them in the production of nanofibers for all-cellulose nanocrystal-based hydrogels and aerogels for a wide range of conventional and high-tech applications. In addition, it is possible to produce a wide range of cellulose nanocrystal reinforced nanocomposites based on injectable polysaccharide hydrogels filled with aldehyde and functionalized cellulose nanocrystals that can simultaneously work both as nanofillers and cross-linkers to provide required level of technical performances to hydrogels produced by using these systems that have many industrial application potentials [161]. For example, in one investigation, hydrogels were produced using this theme that showed highly enhanced elastic moduli (>140% increase at peak strength) along with improved dimensional stability during swelling experimentations and also exhibited strong coherence, while unfilled hydrogels showed degradation over the same time period during experimentations. Besides this, hydrogels produced in this way were also suitable for cell culture and tissue engineering applications [161, 285].

4.4 Cellulose- and Other Polymer-Based Supramolecular Hybrid Hydrogels

Cellulose- and other polymer-based supramolecular hybrid hydrogels have been successful to draw active current research interests for a plethora of potential industrial applications. For example, functional materials like quantum dot (such as CdSe, CdSe/Zns, and CdTe)-doped hydrogels produced by using cellulose or other types of polymers have been actively investigated for different applications including biosensing or bio-labeling. Xie et al. fabricated a fluorescent supramolecular hydrogel by doping with CdTe [286]. In this study, they used mercaptan-ended poly(ethylene glycol)-poly(ε-caprolactone)-based synthetic amphiphilic block copolymer to stabilize colloidal QDs and studied the stability and fluorescent properties of the resultant colloidal QDs. Using a host-guest self-assembly technique between the amphiphilic block copolymers on the QD surface with the addition of cyclic oligosaccharide host molecule (α-cyclodextrin or α-CD), they fabricated a fluorescent supramolecular hydrogel and investigated its physical and chemical

characters (such as spectral properties, rheological characters, gelation kinetics, and mechanical strength). This study showed new prospects to develop biocompatible optical materials with tunable fluorescent properties and mechanical properties suitable for various potential industrial applications [286]. For the first time, Chang et al. successfully fabricated strongly fluorescent hydrogels with quantum dots (CdSe/ZnS nanoparticles) using a mild chemical cross-linking method where CdSe/ZnS nanoparticles were embedded firmly in the cellulose matrices due to strong interactions between the CdSe/ZnS nanoparticles and cellulose after the hydrolysis of QD ligands. The cellulose networks in the hydrogels had a significant contribution to protect the structural integrity and photoluminescent properties of CdSe/ZnS in the hydrogel network. These composite hydrogels (QD-doped cellulose matrix-based hydrogels) showed strong photoluminescent properties that demonstrated different color changes depending on the size of the QDs. In addition, the hybrid hydrogels were transparent and had good compressive strength with a scope to fabricate safe and biocompatible biopolymer-quantum dot-based hydrogels with high level of photoluminescence for different potential applications [287].

4.5 Cellulose Hydrogels for Enzyme Sensing

Palomero et al. fabricated fluorescent nanocellulosic hydrogels based on graphene quantum dots for sensing enzymes (such as laccase) [288]. They developed a novel low-cost fluorimetric platform into the nanocellulosic hydrogel (using sulfur and nitrogen-codoped graphene quantum dots immersed into hydrogels) structure and applied it for the detection of the laccase enzyme. It is novel in the sense that usually used methods generally use catalytic activities for the detection of laccase that depend on surrounding environmental parameters. However, they used the fluorescence response of hydrogels that have graphene quantum dots (or GQDs) which worked as a luminophore for laccase. This type of hydrogels can be easily prepared, and they have enhanced fluorescence signal of GQDs that can avoid their self-quenching with stabilized fluorescence signals with relatively higher level of sensitivity toward laccase. They attributed this behavior to the noncovalent interactions between the sensor and the analyte that caused this significant quenching without peak shifts of GQD fluorescence through energy transfer. It is a simple cost-effective method that can be used to detect and stabilize laccase with a value addition to store and recycle enzymes [289].

5 Hybrid Cellulose Composites and Hydrogels

Both cellulose-based composites and nanocomposites are suitable candidates for different types of advanced composite hydrogel formulations for many potential industrial applications. This type of composite hydrogels provides a very good opportunity to functionalize them using many advanced materials (such as quantum dot, carbon nanotube, cyclodextrin, 2D layered materials, and biomaterials) for both conventional and high-tech applications. A composite or nanocomposite-based

hydrogel has the beauty of the material often derived from the combination of dissimilar entities [131–165, 285–289]. Different other techniques also can be used for the preparation of functionalized composite- and nanocomposite-based hydrogels, for example, (a) composite hydrogel systems doped with functional materials and (b) the functionalized composite or nanocomposite systems for the preparation of hydrogels. In this context, different aspects of quantum dot-doped cellulose nanocomposite systems and their potentials for hydrogel formulations along with their applications are briefly discussed here. Different ways are usually used to produce QD-doped cellulose-based nanocomposites for different industrial applications. For example, Hassan et al. investigated the preparation of new dendronized cellulose derivatives, which were used in the preparation of cadmium sulfide quantum dots/cellulose nanocomposites [106]. In addition, Ruan et al. investigated the preparation and properties of CdS nanocrystals/regenerated cellulose nanocomposites by using in situ synthesizing method during cellulose dissolution in NaOH/thiourea system [107]. Small et al. investigated the preparation of ZnS-doped nanocrystals and mechanical and optical properties of cellulose-ZnS: Cu and cellulose-ZnS: Mn nanocomposites [108]. In addition, Hasan et al. also reported CdS, ZnS, CdS/ZnS, ZnS/CdS (core/shell nanostructures), CdS/ZnS/CdS, and ZnS/CdS/ZnS multilayered nanostructures which were prepared at low temperature using cadmium chloride, zinc chloride, and sodium sulfide in the presence of hyperbranched polyethyleneimine (PEI) polymer. They also reported the method of the preparation of PEI-stabilized nanoparticle-doped functional cellulosic materials which could be used in different optical and electrical applications [109]. From these studies, it was reported that cellulose fibers/semiconductor nanocomposites made from impregnating bagasse pulp fibers and the prepared semiconductor nanostructures exhibited lower-strength properties than blank cellulose fiber sheets despite of the very low fiber loading with the nanoparticles. In addition, the optical properties of different cellulose/semiconductor nanocomposites were close to each other. Loading of cellulosic fiber with the prepared nanostructured semiconductors has no significant impact on the degradation onset temperature but increases the rate of thermal degradation. This kind of nanocomposite and the properties of the interphases have strong influence on the dielectric properties and interfacial polarization of cellulose fiber/semiconductor nanocomposites. All these nanocomposite systems have the potentials to be processed in suitable way to use them in composite- and nanocomposite-based hydrogel formulations for various applications [35, 58–65, 129–185].

5.1 Modification of Hydrogel Properties by the Incorporations of Nanomaterials or Cellulose Nanocrystals into the Structures of Cellulose Composite or Nanocomposites

An important opportunity for the modification of hydrogel properties is simply by the incorporations of different functional materials (such as nanomaterials and cellulose nanocrystals) into the structures of cellulose composite or nanocomposites that are finally used in the hydrogel formulations using particular techniques. For example, different research groups used cellulose and cellulose polymers as a matrix

for nanoparticles for a variety of reasons, including the natural abundance and biodegradability of cellulose. The application of cellulose as a polymeric matrix usually requires either the dispersion or the dissolution of cellulose and the concurrent or subsequent addition of nanoparticles/nanoparticle precursors. As, for example, clay particles have been added to NMMO-based solutions of cellulose, microcrystalline cellulose (MCC)-hydroxyapatite nanocomposites were synthesized by using a microwave assisted, one-step reaction where $CaCl_2$, NaH_2PO_4, and MCC were added to *N, N*-dimethylacetamide solvent. CdS particles were prepared in NaOH/urea cellulose solutions and the regenerated cellulose films cast from the dispersion which showed the optical properties of CdS. In addition, all-cellulose nanocomposites were prepared by the selective surface dissolution of bacterial cellulose sheets and by the electrospinning of core-shell fibrous mats in which CNCs were sheathed by a shell composed of regenerated cellulose. There are a number of reports on the in situ synthesis of nanoparticles within solid cellulose scaffold, for example, (a) the preparation of superparamagnetic nanocomposite films by synthesizing iron oxide (Fe_2O_3) nanoparticles within the pores of regenerated cellulose films; (b) the production of wet spun cellulose fibers from solution in NaOH/urea/H_2O, followed by treatment in $FeCl_3$ and NaOH in order to generate iron oxide particles using in situ technique; and (c) the preparation of $CaCO_3$ cellulose nanocomposites by synthesizing $CaCO_3$ nanoparticles in the presence of hardwood bleached Kraft pulp and carboxymethylated cellulose fibers [106–126]. The limited solubility of the cellulose curbs the applicability of cellulose nanocomposites, despite the successes achieved from using cellulose to prepare interesting and functional nanocomposites.

In this context, cellulose derivatives, which are soluble in solvents ranging from water to nonpolar organics, are more versatile and have the potential for improved compatibility with nanoparticles. Cellulose acetate has interesting properties, such as (a) transparency, (b) flexibility, and (c) easy processability. It has been used for the production of cellulose-based nanocomposites, for example, (a) melt intercalation of polymer, (b) extrusion followed by either injection or compression molding to create cellulose acetate-clay nanocomposites, and (c) incorporation of TiO_2 particles into CA films in order to promote the enzymatic biodegradation of CA by cellulose. Carboxymethyl cellulose (CMC), a water-soluble cellulose derivative, has been reported to stabilize ZnO nanoparticle dispersions in glycerol plasticized-pea starch. CMC has also been used as the matrix in pH-sensitive superabsorbent nanocomposites containing attapulgites, in nanocomposites containing metals (Cu, Ag, In, and Fe), and in hydrogels cross-linked with poly(*N*-isopropylacrylamide) which contained clay [110–114, 125, 126]. So, this type of modified composite and nanocomposites is interesting candidate for cellulose-based hydrogel formulations for different specific industrial applications.

5.1.1 Modifications of Polymer Characteristics by the Incorporation of Cellulose Nanocrystals in Different Polymer-Based Composites and Nanocomposites and Their Uses in Hydrogel Formulations for Various Industrial Applications

Different ways can be used to modify the characteristics of composite or nanocomposites, for example, by incorporating cellulose nanocrystals in structural compositions of composites and nanocomposites, and these modified systems can then

be used for the fabrication of hydrogels for various industrial applications. The interesting properties of cellulose nanocrystals (CNCs), such as the high strength, high aspect ratio, and huge surface area, have the potential to significantly improve the mechanical properties of nanocomposites at low CNC filler loadings. Percolation theory has been used to state the surprising reinforcement effects observed at low loadings of fibrous elements. Mechanical properties (e.g., strength and modulus) are optimal at or above the percolation threshold, where each CNC is, on average, in close contact with two others and a rigid, 3D, hydrogen-bonded network is formed within the polymeric matrix [113]. As with all nanocomposite materials, the main challenges are (a) the uniform dispersion of CNCs and (b) achieving good interfacial adhesion between CNCs and matrix, particularly if hydrophobic. Generally, CNC nanocomposites are either processed into films, by solvent casting, or fibers/fibrous mats, by electrospinning. Electrospinning is very promising due to the alignment of CNCs in the fibers which can enhance axisymmetric properties. One of the most straightforward methods for the preparation of polymeric nanocomposites which contain CNCs is the direct addition of CNCs into either a pre-polymer or polymeric solution. In order for a successful approach in this method, the CNCs must show dispensability in the polymeric phase.

CNCs synthesized from sulfuric acid hydrolysis which show colloidal stability in water are suitable for direct addition to an aqueous system, for instance, some CNC-based nanocomposites (which depend on the aqueous stability inherent to sulfuric acid hydrolyzed samples) are (a) films cast from mixtures of CNCs and aqueous poly(oxyethylene) solutions, (b) films of oriented CNCs in a polyvinyl alcohol (PVA) matrix prepared by application of a 7T magnetic field during solvent evaporation, (c) fibrous mats electrospun from CNCs dispersed in aqueous PVA, and (d) films cast from CNCs which were dispersed in aqueous polyurethane solutions. Different methods are often used to disperse CNCs in nonaqueous media (such as hydrophobic solvents and polymeric matrices), some of which are (a) vigorous sonication to disperse freeze and/or vacuum dried CNC powders in solvents (e.g., ethanol), furfuryl alcohol, formic acid, *N,N*-dimethylformamide (DMF) [76–78, 135–141], or dimethyl sulfoxide (DMSO), which are compatible with a pre-polymeric/polymeric matrix, (b) the use of a surfactant, (c) solvent exchange of water for organic media such as toluene or DMF, and (d) surface grafting reactions to improve CNC compatibility with hydrophobic polymers. Different research groups have achieved some degree of success with each of these methods. However, the drying of CNCs results in aggregation and is very difficult to obtain; a complete reversion on re-dispersal remains uncertain whether graded solvent exchanges are truly able to produce stable CNC dispersions in organic media. For example, the stability of freeze-dried CNCs re-dispersed in polar organic solvents (e.g., DMF, DMSO) was attributed to the presence of residual water (~0.1%). Besides this, the surface modification of the CNCs is challenging due to limited dispersibility of CNCs in organic reaction media which is required to be surface specific in order to retain the colloidal nature of the particles. Additionally, the characterization of the modified product is also challenging due to the limitation of the use of usual techniques to colloidal particles; otherwise they may not possess the degree of

sensitivity required to detect changes in surface groups which represent a small fraction of total atoms. As a result, direct observation of surface-modified CNCs is rarely reported in the literature but is instead inferred from observed changes in fundamental characteristic properties (e.g., stability, dispersibility, charge, the presence or absence of LC ordering). Research in this area is still in the initial stage, and it is expected that in the near future, suitable techniques for reliable production of stable dispersions at the percolation threshold will be discovered, as they are essential to produce homogeneous CNC-reinforced hydrophobic nanomaterials [123–126, 135, 136]. It is highly envisaged that cellulose nanocrystal can be used along with quantum dots, and this combination can be used to dope a range of natural and synthetic polymers and processed accordingly for producing electrospun fibers from these doped polymers for a variety of applications. Electrospun nanofibers are popular as fillers for both composite and nanocomposite systems which can be processed to be used in hydrogel formulations. Additionally, electrospinning technique can also be used for fiber formations from certain type of specially designed hydrogels. Co-electrospinning technique has the feasibility to produce different composite scaffolds from polymer mixtures containing both hydrogels and solution or dispersion of another polymer for producing special type of scaffolds with selective targeted applications. Besides this, ultrashort protein fibers or similar type of biological or particular type of polymer-based fibers produced by electrospinning can also be directly used as special type of component in hydrogel fabrications [1–16, 131–171, 248–253, 255].

5.1.2 Future Trends in the Developments of Functional Material (Such as Quantum Dot-Doped Polymers) and Cellulose Composite- and Nanocomposite-Based Hydrogels for Specific High-Tech Applications

Cellulose composites and nanocomposites have an increasing tendency of functionalization using a wide variety of materials, and they can also be extended for hydrogel formulation for large-scale industrial explorations for many interesting properties. Some of these properties include (a) the natural abundance of raw materials, (b) renewability, (c) low cost, (d) biodegradability, (e) biocompatibility, (f) low density, (g) outstanding elastic modulus (of such polymers), and (h) environmentally benign in character. These are some of the most important characters from different industrial points of view. In terms of functionalization, new materials evolve by the day due to tremendous advancement in different areas of science and technology. For example, new generation of 2D layered materials and nanotubes, advanced fluorescent materials, stimuli-responsive materials and polymers, polymer dot, carbon dot, and quantum dot is being targeted for the future focused advanced use of these materials. For instance, different selective features of quantum dot-doped cellulose-based hydrogels and their future application trends are discussed here.

Many future materials and devices based on QDs require their incorporation and organization in polymeric matrices (such as synthetic polymers, natural polymers like cellulose, and cellulose composites as additives). As a result, there is a growing need for photonic materials and devices which provide the required encouragement

to the development of many different strategies to produce polymer/QD hybrid structures. The appropriate selection of a strategy depends primarily on the final application of the hybrid materials. For example, if the material is targeted for biological applications, in addition to its luminescence efficiency, the compatibility of the material with the biological systems is very important (such as some cellulose products show biocompatibility and are suitable to be used in biological applications when incorporated with quantum dots). The fabrication methods which have been reported to date have many merits and demerits. As a result, the development of new routes for the production of QD/polymer nanohybrid materials (e.g., quantum dots doped in the composition of cellulose and another suitable polymer-based nanocomposite) is a very important research topic as the simultaneous control over the size and shape of the matrix and over the amount, spatial distribution/localization, separation, and orientation of the QDs within the matrix still remains a challenge to be solved. In this context, it is important to note that an important study on flexible luminescent CdSe/bacterial cellulose nanocomposite membranes has been reported [290]. They successfully fabricated flexible luminescent membranes based on bacterial cellulose (BC) by using the in situ synthesis of the CdSe nanoparticles on the BC nanofibers [297]. By using X-ray diffraction (XRD) patterns and field emission scanning electron microscopy (FE-SEM), they observed that CdSe nanoparticles were homogeneously dispersed on the BC nanofibers. They also observed that the thermal stability of BC was greatly increased with the inclusion of CdSe nanoparticles. In addition, they noted that the CdSe/BC nanocomposite exhibited good photoluminescent properties and excellent mechanical properties. This study provided an effective method for the construction of flexible BC membranes with photoluminescent properties, which have promising application potentials in the fields of security papers, sensors, and flexible luminescent membranes. Additionally, the introduction of colloidal quantum dots into cellulose and other suitable polymer-based nanocomposite structures using different techniques including electrospinning technique provides many opportunities due to their potential industrial application potentials. For example, colloidal quantum dots (QDs) have garnered much attention in the recent times due to their attractive spectral properties leading to a wide range of potential applications in bio-imaging/sensing, display, telecommunication, and quantum cryptography. The colloidal QDs allow spin-coating-based processing, possibility of self-assembly, compatibility with silicon platform, and tunability in absorption and emission spectra and have become one of the most attractive nanoscale fluorescent emitters. While colloidal QDs have become one of the most attractive nanoscale fluorescent emitters, they have still not found widespread application in practical photonic devices. This is in part due to the difficulty in incorporating these QDs into photonic structures. In addition, practical ultrafast all-optical switches, modulators, flexible emitters, and room temperature single-photon sources using these QDs can be realized if they can be patterned into waveguide or microcavity structures. Recently there have been several attempts to achieve this goal by embedding QDs in a variety of photonic structures and hosts [86–100, 127–130]. A significant challenge here is the incorporation of QDs into transparent host matrices without affecting their optical properties [101–103,

127–130]. The achievement of monodispersity, high fill factor, and efficient charge injection is highly desired. In addition, embedding photon emitters in microcavities alters their emission properties due to the ability of these structures to confine and enhance electromagnetic fields. Recently, there have been several attempts to achieve this goal in QDs by embedding them in poly(methylmethacrylate) (PMMA) spheres, silica microspheres, one-dimensional microcavities, two- and three-dimensional photonic crystals, and microdisk structures [86–100]. Most of the one-dimensional microcavity structures reported to date have used sputtered or thermally evaporated distributed Bragg reflector (DBR) mirrors. While they do give good reflectivity, often they have undesirable effects on the optical properties of the QDs through surface defects. In addition, these techniques also require multiple deposition systems. Hence, it is highly attractive to develop a low-cost technique for the fabrication of the microcavities which is compatible with the solution processing of the colloidal QDs. In addition, solution processing allows the fabrication of the microcavity on a wide variety of substrates including flexible ones (such as cellulose, paper, and cellulose composites). Besides this, there are studies which report the realization of a one-dimensional microcavity laser using colloidal InGaP quantum dots as the gain medium fabricated using spin coating and the development of photonic integrated circuits using colloidal CdSe quantum dot composites fabricated through soft lithography. These studies also discuss the effect of the host matrix on the luminescent properties of the QDs using steady-state and time-resolved luminescence measurements. Currently, polymer composites based on natural fillers (such as cellulose, natural polymers, etc.) have been successful to attract active research interest as alternative materials to glass- or synthetic fiber-reinforced plastics in several applications, mostly for automotive, appliance, and packaging products. In this case, one of the major advantages of using natural fibers is that these are biodegradable and renewable and exhibit low cost, low density, and high toughness. However, the low compatibility between fibers and polymer matrix contributes to the weak mechanical performances which limit the use of these materials. Surface modification of the fibers and/or polymer functionalization, as well as addition of compatibilizers, is usually required to improve the interfacial interactions between the components. In addition, when a quantum dot is used in order to make composite materials for advanced applications, a special care is needed to ensure that the functional behaviors are properly retained after the incorporation of quantum dots into the nanocomposite structure and their use in hydrogel fabrications using appropriate steps and techniques. This type of materials can also be used for aerogel fabrications. For example, photoluminescent cellulose aerogels of variable shape containing homogeneously dispersed and surface-immobilized alloyed $(ZnS)_x(Cu\text{-}InS_2)_{1\text{-}x}/ZnS$ (core/shell) quantum dots (QDs) have been reported by using different techniques, some of which are (a) dissolution of hardwood pre-hydrolysis Kraft pulp in the ionic liquid 1-hexyl-3-methyl-1H-imidazolium chloride, (b) addition of a homogenous dispersion of quantum dots in the same solvent, (c) molding, (d) coagulation of cellulose using ethanol as antisolvent, and (e) supercritical carbon dioxide ($scCO_2$) drying of the resulting composite aerogels [107]. Wang et al. achieved both compatibilization with the cellulose solvent and

covalent attachment of the quantum dots onto the cellulose surface through replacement of 1-mercaptododecyl ligands typically used in synthesis of $(ZnS)_x(CuInS_2)_{1-x}$/ZnS (core-shell) QDs by 1-mercapto-3-(trimethoxysilyl)-propyl ligands. They also obtained cellulose – quantum dot hybrid aerogels where apparent densities were from 37.9 to –57.2 mg cm^{-3}. In addition, their BET surface areas range from 296 to 686 m^2 g^{-1} comparable with non-luminescent cellulose aerogels obtained via the NMMO, TBAF/DMSO, or $Ca(SCN)_2$ route. They also observed that depending mainly on the ratio of QD core constituents and to a minor extent on the cellulose/QD ratio, the emission wavelength of the novel aerogels could be controlled within a wide range of the visible-light spectra. They also observed that higher QD contents led to bathochromic PL shifts and a hypsochromic shift with an increase in the amount of cellulose at constant QD content. In addition, the reinforcement of the cellulose aerogels and hence significantly reduced shrinkage during $scCO_2$ drying is a beneficial side effect when using α-mercapto-ω-(trialkoxysilyl) alkyl ligands for QD capping and covalent QD immobilization onto the cellulose surface [104]. This type of functionalized cellulose composites has the potentials for advanced hydrogel or aerogel fabrications for many high-tech applications. For example, when the respective QDs are furnished with suitable functional groups grafting QDs onto the large surface of aerogels, it is possible that they can form covalent linkages with the solid aerogel network structure. In addition, synthesis of QDs through thermolysis in high boiling solvents is commonly accomplished by simultaneous introduction of nonpolar, hydrophobic ligands to support surface deactivation for preventing QDs from agglomeration which would negatively impact their photoluminescent properties. Hence covalent immobilization of QDs on the surface of solids requires the introduction of moieties that carry respective anchor groups which can be achieved either by inclusion of hydrophobic QDs into amphiphilic micelles leading to an interdigitated bilayer or by ligand replacement [104]. This type of cellulose-based gels is envisaged that can be made suitable to produce quantum dot-doped electrospun nanofibers using proper adjustment of chemistry, rheology, and electrospinning methods [127–130]. Moreover, cellulose-based quantum dot-doped electrospun nanofibers can be used in particular type of composite hydrogel fabrications which are useful for light-emitting purposes with potential use in lab-on-a-chip devices and also in optical sensing applications [6, 131–174, 248–272].

Electrospun polymeric nanofibers and their incorporation in different composite systems including hydrogels are attracting burgeoning interest as innovative nanoscale structures, exhibiting peculiar, smart properties useful for many applications, including sensing, tissue engineering, optoelectronics, and photonics [255–272]. In addition, the interest toward this class of nanomaterials relies on their physicochemical properties, on their high-surface-to-volume ratio, and on the availability of low-cost production techniques. Among different techniques, electrospinning offers a valuable compromise between throughput and control of the nanostructure composition, shape, and size. Hence, the application of the use of this technique in different aspects of hydrogel fabrications has some real significance in different areas. For example, the high stretching of the liquid jet using the electrospinning process can lead to anisotropic physical properties of the collected nanofibers and to

enhanced optical and electronic features because of the peculiar macromolecular packing within the electrospun fibers. As emerging field, the development of light-emitting electrospun nanofibers for optoelectronics and photonics can be employed by using either optically inert polymers doped with low-molar-mass fluorescent molecules (typically organic dyes), inorganic quantum dots, etc. or organic semi-conducting polymers or particular type of composite- or nanocomposite-based hydrogel systems. Hydrogel systems doped with polymeric nanomaterials have potential applications as submicron light sources, as waveguides, as active components of lasers and transistor devices with electrooptical interplay, and as nanoscale sensing elements with potentials for different industrial applications [6, 118, 161, 182–184, 248–285].

6 Selected Industrial Applications of Cellulose-Based Hydrogels

Cellulose-based superabsorbent hydrogels have a wide range of industrial applications. Some of the products are commercially available in the market, while some others are in the process of making their way into the market. A good number of patents relating to cellulose-based superabsorbent hydrogels have been granted for a wide range of applications where the main applications include (a) personal hygiene products, (b) water reservoir for agriculture, (c) drug delivery and other biomedical applications, and (d) separation membrane (as many promising applications such as protective barriers for volatile organic compounds spilled in the environment and as absorbents for waste oil) [28]. Some of these uses are briefly presented in Fig. 1 in a diagram where several selected applications of cellulose-based hydrogels are illustrated.

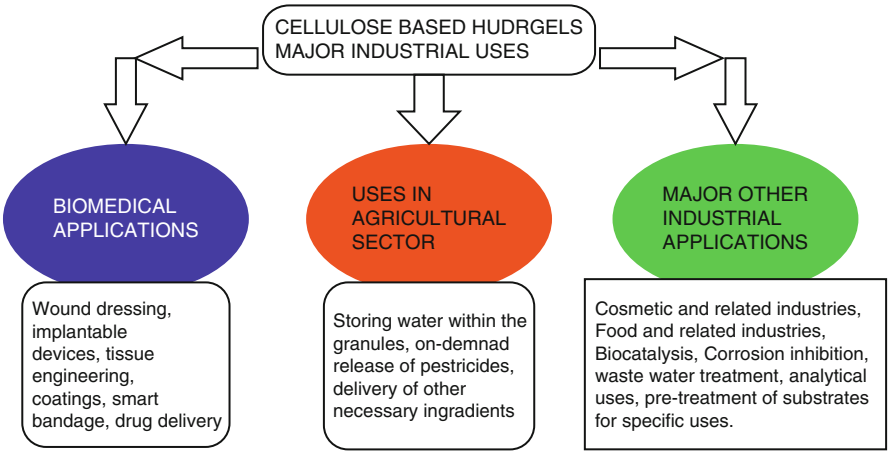


Fig. 1 Diagrammatic presentation of selected applications of cellulose-based hydrogels

6.1 Applications in Agricultural Sector

Cellulose-based superabsorbent hydrogels have the capability to retain enormous quantity of water in their structure which can be a blessing to the agricultural sectors in different part of the world where there is a chronic shortage of water especially in the area of irrigation and other similar uses. Many studies focused on the uses of cellulose-based superabsorbent hydrogels for enhancing the conditions of soils and related other properties which include (a) the changes of water content, (b) microbial activity of soil, and (c) comparative study on the nature of the crop yield from the soil before and after treatment with biomass. For example, one of the similar investigations revealed that the use of cellulose-based superabsorbent hydrogels was useful to the physical properties of the soil that contributed in crop yield [29]. A separate study observed the impact of the controlled uses of water resources in agriculture where cellulose-based superabsorbent hydrogels were rigorously studied for their efficient storage and a sustained release of water to the soil and plant roots and illustrated the potential use of superabsorbent hydrogels as water reservoir for controlled applications in agriculture [30]. Cellulose-based superabsorbent hydrogels can be used as carriers for pesticides which have many economic and sustainable implications in agricultural sector due to the possibility to encapsulate herbicides into the structure of the hydrogels in order to have effective influence on the release of herbicides. It is one of the cost-effective ways to control pest and weed in agriculture to avoid potential adverse environmental impacts [31]. For example, similar other related studies also focused on the uses of cellulose-based superabsorbent hydrogels on agriculture [32–34].

6.2 Personal Healthcare

One of the most common uses of superabsorbent hydrogels is in the field of personal healthcare since they can absorb and contain large amounts of fluid (e.g., urine, blood, secreted fluid from wound). Some of the usually used hygiene products include (a) disposable diapers, (b) female napkins, and (c) special type of absorbing materials used in wound dressing [4]. Currently, most widely used superabsorbent hydrogels for producing sanitary napkins are mainly based on acrylic acid- or acrylamide-based products, but they have a number of limitations including (a) higher cost, (b) poor biodegradability, and (c) less environmentally friendly. However, there are quite a few reports to enhance the quality of hydrogels and also overcome the limitations. For example, Liu et al. incorporated flax yarn waste into the structure of superabsorbent hydrogels suitable to use and develop sanitary products (such as sanitary napkins) with relatively higher level of biodegradability, superabsorbency, and fluid retention capability [35]. Over the times, relatively more convenient and comfortable disposable healthcare products have been developed, and now some of them are commercially available [36–38]. However, no commercially developed products are available in the market which show complete

biodegradability; thus, cellulose-based superabsorbent hydrogels may provide some future product which can overcome some of these limitations.

6.3 Water Treatments

Cellulose-based superabsorbent hydrogels provide the opportunity to be used in water purification by removing pollutants (such as heavy metals) from the water sources and also by separating certain elements of the contaminated water. In order to carry out this type of activities, hydrogels are usually functionalized, for example, Zhou et al. synthesized novel magnetic hydrogel beads by blending chitosan with amine functionalized magnetite nanoparticles, carboxylated cellulose nanofibrils, and polyvinyl alcohol using instantaneous gelation technique. The resultant magnetic hydrogel beads showed the capability to absorb lead ions from polluted water due to the presence of numerous carboxylate groups and abundant hydroxyl and amino groups in the composite functionalized hydrogel structure [39]. Many other reports also indicated the scope of water purification to some extent using cellulose-based superabsorbent hydrogels [40–42]. However, new strategies are still required to develop water treatment using cellulose-based superabsorbent hydrogels.

6.4 Biomedical Applications

Cellulose-based superabsorbent hydrogels are good candidate, when biodegradability of a hydrogel is required or recommended because of their interesting properties including (a) low cost, (b) availability in large quantity, (c) biocompatibility, and (d) stimuli-responsive behaviors of some cellulose and their derivatives (present in the hydrogel) when exposed to external stimuli. In fact, cellulose-based superabsorbent hydrogels are frequently used in different areas of biomedical field, some of which include in drug delivery, tissue engineering, cell bioreactors, and micropatterning neural cell cultures. For example, He et al. fabricated the onion-like, multilayered tubular cellulose-based superabsorbent hydrogels. This study showed that the L929 cell could survive and proliferate in the larger interior space of the multilayer cellulose-based superabsorbent hydrogels which proved a great potential biomedical application [34]. Many similar studies also showed the practical and potential biomedical applications [34, 49, 50, 70–84].

6.5 Miscellaneous Industrial Exploitations

Besides the usual applications of cellulose-based superabsorbent hydrogels in hygienic and bio-related and agricultural uses, they also have applications in other areas including (a) pharmaceutical dosage forms; (b) separation technology; (c) textile, leather, and paper industries (such as in wastewater treatment); (d) water-swelling rubbers; (e) soft actuators/valves; (f) electrical applications; (g) construction,

packaging, and artificial snow; (h) sludge/coal dewatering; (i) fire extinguishing gels; and (j) sensoric materials. In addition, many new advanced technologies are surfacing by the day which have industrial application potentials [6, 35, 61–64, 127–185, 248–272, 285–289, 297].

7 Future Trends and Perspectives in the Applications of Cellulose-Based Hydrogels

Different selected aspects of superabsorbent hydrogels based on cellulose have been briefly discussed within this chapter. Cellulose-based superabsorbent hydrogels show some attractive characters that include (a) hydrophilicity, (b) biodegradability, (c) biocompatibility, (d) transparency, (e) low cost, and (f) environmentally friendly. As a result, this type of hydrogels is popular for various industrial applications which include (a) biomedical applications, (b) applications in the human body, (c) water purification, (c) applications in agriculture and horticulture, (d) personal healthcare, (e) water treatment, and (f) biomedical applications. The trend in future research on cellulose-based superabsorbent hydrogels is mainly focused on the design of novel materials and product in order to cater demands for different desired properties and also to demonstrate new functionalities with higher performances. These functional characters are likely to enhance their capacity to make them suitable for various applications including electronics and catalysis and also as chemical and biomedical sensors. In industrial applications' point of view, cellulose-based superabsorbent hydrogels provide a new extended field of research to design and realize enhanced cost-effective product performance with respect to a number of areas including (a) biocompatibility and biodegradation, (b) higher mechanical, and (c) environmentally benign characteristics. In addition, another current research trend is to develop cellulose-based environmentally friendly cost-effective products with a desired design capability to replace available petroleum-based products in the foreseeable future. Continuous active research activities relating to cellulose-based superabsorbent hydrogels will contribute to realize this type of products in the near future [1–16, 131, 161, 248–272, 284–289].

Hydrogels based on cellulose composite and nanocomposites have also seen a notable upsurge in continuous active research activities for a wide range of industrial application potentials. During the past several decades, hydrogels and nanoparticles have already exerted a dramatic impact in biological, biomedical, pharmaceutical, and diagnostic fields. However, their some intrinsic shortcomings severely restrict their practical applications. Significant efforts have been paid to improve the performance of hydrogels and NPs. The fabrication of composite materials by combining two or more components in a single entity can surmount individual shortcomings and give rise to synergistic functions that are absent in the individual components. The incorporation of NPs in three-dimensional polymeric hydrogel matrix as an innovative means to obtain nanocomposite hydrogels with improved properties and multiple functionalities has gained enormous attention in many areas. On the basis of this review, we can found that various types of NPs, such as carbon-based NPs, silicon-based NPs, metal NPs, and polymeric NPs, are combined with the polymeric

hydrogel network to create multicomponent systems. The porous structure and free space within the hydrogel networks can not only provide an ideal hydrated environment for the stabilization of NPs without aggregations or disintegration and the protection of NPs from degradation or denaturation but also work as a reservoir to localize NPs at the target site. More importantly, the coatings of hydrogels around the NPs endow a hydration layer, which often is an essential prerequisite for the biomedical and biological applications of inorganic and metal NPs, as the hydration layer can significantly improve the biocompatibility and reduce the cytotoxicity [1–16, 71, 104–149, 255–269].

On the other hand, the incorporation of NPs into hydrogels can not only markedly improve their mechanical, elastic, and adhesive properties as well as physicochemical and thermal stability but also promote the cell attachment and proliferation and improve drug loading capacity and drug release profiles. More significantly, the encapsulation of carbon, metal colloidal particles or quantum dots into polymer hydrogel networks will impart them with exclusive thermal, sonic, optical, electrical, or magnetic properties, which are not achieved by individual polymeric systems and are highly appropriate for various applications, especially for therapeutic and diagnostic applications. Apparently, the benefits of the combination of NPs and hydrogels have resulted in generation of a new class of advanced materials with unique properties that have a wide spectral range of biomedical applications, ranging from controlled drug delivery depots, cell and tissue adhesive matrices, wound dressing and tissue engineering scaffolds, stem cell engineering and regenerative medicines, biosensors, actuators, and other biomedical devices. However, despite the vast potential applications of nanocomposite hydrogels in biomedical fields, there are still lots of challenges to be overcome before they can be applied in clinical use. For example, the improved performance of the nanocomposite hydrogels is mainly ascribed to the enhanced interactions between the NPs and polymer chains. Therefore, apart from particle parameters, the quantity and homogeneity of NP integration are still a matter of concern. To obtain excellent performance, NPs should be abundantly and homogeneously dispersed within the hydrogel matrix. However, due to a large surface area, hydrophobic NPs physically embedded in the hydrophilic polymer matrix often tend to aggregate, leading to the failure of anticipative enhancement of properties. Therefore, there is still a need to elucidate the mechanisms and interactions between NPs and polymer chains inside the nanocomposite hydrogels, and the simple, cost-effective, scalable, and reproducible preparations of nanocomposite hydrogels with desirable properties need to be investigated thoroughly. Apparently, the nanocomposite hydrogels combining the individual functions of NPs and hydrogels are ideal candidates for multimodal drug delivery platform with simultaneous capabilities in drug encapsulation, targeting delivery, photothermal therapy, and in vivo imaging. This synergistic performance is usually not be achieved by an individual. However, the more detailed pharmacological studies need to demonstrate the therapeutic efficacy and biological responses. In addition, most of the nanocomposite hydrogels have been performed only in vitro. Therefore, in future studies, the detailed performances (gelation time, swelling, elastic modulus, responsivity and functionality), long-term toxicity and biodegradability, as

well as the biological properties such as protein adsorption, cell adhesion, tissue compatibility, and whole-body effect of such hydrogels under in vivo conditions should be clearly addressed. In summary, there should be a coordinated and comprehensive research to establish fundamental interactions among nanoparticulate materials, hydrogel matrices, and biological systems, before hydrogels will become practical and useful in this exciting field. All these challenges will drive the effective collaboration of scientists from the fields of chemistry, materials, engineering, biology, medicine, and nanoscience. We look forward to seeing many exciting research accomplishments in this burgeoning field of bio-related nanocomposite hydrogels [161, 254–272, 284–289]. In addition, electrospun cellulose nanofibers have many exciting potential applications as reinforcements in nanocomposites and their applications in cellulose-based hydrogel fabrications in association with other natural and synthetic polymers in hybrid systems. These types of hybrid systems have a great variety of application potentials as very important materials where some of which include (a) materials for robust structures, (b) hierarchical materials, (c) electronic display materials, and (d) materials for energy harvesting. The potential mechanical properties of cellulose nanofibers compete well with other engineering materials and have many useful high-end technological applications. Proper dispersion of cellulose or other components of the cellulose-based nanocomposites is one of the critical steps in the production of cellulose nanocomposites and their use in the hydrogel fabrication for desired applications. For example, the layer-by-layer deposition technique offers a facile route to overcoming this, with remarkable percolation of cellulose nanowhiskers interacting with each other, and with the surrounding matrix, in a way that greatly improves the mechanical properties of the resultant material (such as when quantum dot-doped cellulose is also used as one of the constituents in the cellulose nanocomposite structure). Additionally, there are also some issues with the toxicity of quantum dots. However, many pieces of active research are going on in order to overcome these drawbacks. Besides this, cellulose nanowhiskers have a high-surface-area-to-volume ratio where the surface plays a vital role in not only the mechanical efficiency of stress transfer in a nanocomposite but also the ability to modify the surface chemistry. By grafting quantum dots to the surface of cellulose nanowhiskers, it may be possible to utilize self-assembly methods to generate new forms of composite biomaterials for a variety of applications (including biosensing, security, electronic display, and sensitive membranes for wastewater treatments). When the surface of nanowhiskers is chemically coupled with chromophores, it provides a route for successive dispersion of cellulose nanowhiskers in nanocomposite materials, and TEMPO oxidation also proves a means for isolating nanofibers. Similar type of technique can be used for chemical coupling of the surface of nanowhiskers using suitable quantum dots for a wide range of applications. Bacterial cellulose (BC) nanofibers are useful for the generation of hierarchical composites which offers a way for long micrometer-sized fibers for an effective use in composites by improving coupling between the fiber surface and the surrounding resin. BC nanofibers have also been shown to be useful for the generation of optically transparent and flexible composite films with low thermal expansion coefficients. Additionally, by the combination of these high stiffness fibrils with a cellulose matrix, excellent mechanical

properties can be achieved for all-cellulose nanocomposites which can be further functionalized with the use of functional materials such as quantum dots for high-tech applications. This chapter has attempted to provide some specific information on the behavior of quantum dots and their applications along with the scope of doping them into polymers using different techniques using a special emphasis electrospinning technique and the use of quantum dot and cellulose for many advanced uses. This chapter has provided some very useful information on the scope and uses for quantum dot-doped cellulose nanofibers and their potential advanced applications in both composite- and nanocomposite-based hydrogels or as active components of the hydrogel where active current research is going on to realize the practical industrial application potentials. So, in the near future, we will see quite a lot of new progresses in the use of quantum dot-doped cellulose nanofibers or similar other functional material-based advanced systems for their applications in composites, nanocomposites, and hydrogel fabrications which can effectively overcome many of the current practical difficulties [1–16, 30–47, 131–161, 194–205, 254–259].

Lastly, cellulose-based hydrogels are biocompatible and biodegradable materials which show promise for a number of industrial uses, especially in cases where environmental issues are concerned, as well as biomedical applications. Several water-soluble cellulose derivatives can be used, singularly or in combination, to form hydrogel networks possessing specific properties in terms of swelling capability and sensitivity to external stimuli. The current trend in the design of cellulose hydrogels is related to the use of nontoxic cross-linking agents or cross-linking treatments, to further improve the safety of both the final product and the manufacturing process. The smart behavior of some cellulose derivatives in response to physiologically relevant variables makes the resulting hydrogels particularly appealing for in vivo applications. In spite of the non-bioresorbability of cellulose, the possibility to functionalize cellulose-based hydrogels with bioactive and biodegradable extracellular matrix domains suggests that in the near future, such hydrogels might be ideal platforms for the design of scaffolding biomaterials in the field of tissue engineering and regenerative medicine [1–16, 35–76, 195–205, 224–247].

8 Conclusion

Different selected aspects of superabsorbent hydrogels based on cellulose have been briefly discussed within this chapter. Cellulose-based superabsorbent hydrogels show some very attractive characters suitable for a wide range of industrial exploitations. This chapter has selectively covered some of these most commonly used industrial applications of cellulose-based hydrogels. Due to the limitation of the scope of this current chapter, detailed discussions on various aspects of different industrial applications are carefully avoided. However, some updated information along with references have been provided on different aspects of these industrial uses of cellulose-based hydrogels in order to provide more detailed information for interested readers.

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Cellulose-Based Absorbents for Oil Contaminant Removal

30

Wang Liao and Yu-Zhong Wang

Contents

Abstract

With the rapidly increasing exploitation, transportation, and utilization of fossil oils, oil spillage accidents occur frequently worldwide. Oil pollution can lead to a serious loss of valuable resources on coastal and marine ecosystems during a long period. Besides, industrial waste oil may have a broad impact on city ecological

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environments and human health. It is thus urgently required to solve oil pollution efficiently. Generally, current strategies are classified into three groups: (1) burning the oil spill in situ, (2) dispersing the oil in water by adding dispersants to facilitate nature degradation, and (3) extracting the oil from the water. The last method seems the "greenest" because both the absorbent and the oil can be recycled. Among the absorbents, cellulose-based absorbents are the first choices due to their environmental friendliness of renewability and biodegradability, good mechanical properties, low density, high porosity, high absorption capacity, and cost-effectiveness. In this chapter, we intend to demonstrate the following aspects of cellulose-based absorbents, including (1) raw materials: properties and pretreatments, (2) fabrication of the various absorbents, (3) characterization of the structure and properties, (4) cellulose-related absorbents and other applications, and (5) discussions and future scope. This work aims to draw a full outline of the cellulose absorbents to date and to promote the understanding and developing of these materials in the future.

Keywords
Cellulose · Aerogel · Absorbent · Absorption · Oil · Hydrophobic

1 Introduction

Fossil oils are one of the most available fuels with high-energy density. For this reason, people have been exploring fossil oils from every corner of the world. However, the source sites are always far from the using sites which are globally located; long-distance transportation is thus necessary, during which oil leakages because of fracture, natural calamities, and/or human error are almost inevitable. It has been estimated that 224,000 tons of oil from the spillage of oil tankers were released into the sea globally in the first decade of the twenty-first century [1]. The most striking leakage event that recently happened is the Deepwater Horizon oil spill (2010) in the Gulf of Mexico. This event is considered the largest marine oil spill in the history of the petroleum industry, which lasted 87 days, killed 11 people, and leaked ca. 3.19 million barrels of oil into the gulf. Although the leakage was finally stopped, the resulting pollution will affect underwater and shoreside ecosystems for a long period [2, 3]. Additionally, industrial waste water, which probably contains waste oil, is discharged into rivers, lakes, and seas, again, seriously affecting environments and life health. Based on the fact that 1 l of benzene will make several million gallons of water unfit for drinking, the environmental threat of oil pollutants is extremely serious [4]. Furthermore, because of offensive sights and odor, oil-contaminated waters deteriorate the investments and tourism of the vicinity [5]. It is therefore extremely urgent to solve the problems of leakage oil on water.

At present, the cleanup methods are either physical or chemical [6, 7]. The physical methods include skimming, booming, and absorbing. And the chemical methods include bioremediation and in situ combustion [8]. But for the rinsing-

Table 1 Comparison between the oil cleanup methods [14] (Copyright © 2017, American Chemical Society)

Methods	Advantages	Disadvantages	Environmental concerns	Cost
In situ burning	Quick	Environment and safety concerns	Formation of large quantities of harmful smokes and viscous residues after combustion	Cheapest
Mechanical, e.g., skimmers, booms	Efficient	Labor-intensive, time-consuming	Friendly	Very expensive
Chemical, e.g., dispersants, solidifiers	Simple	Low or no efficiency for viscous oil and in calm water	Being harmful to aquatic organisms	Expensive
Bioremediation or microorganism degradation	Efficient	Ineffective in spill with large coherent mass	Friendly	Cheap
Absorption	Efficient, simple, less secondary pollution	Labor-intensive	Friendly, the biodegradability depends on the raw materials	Cheap

drying [9, 10], distillation [11], or combustion [12, 13], additional energy is consumed, and new pollution is simultaneously generated. By comparison, using absorbents is the most promising method because both the absorbing material and the oil can be recycled by simply squeezing, making it economic, efficient, and less polluted [1]. Detailed comparison is listed in Table 1.

To date, existing absorbents include [1] inorganic materials, such as clays [15–17], fly ash [18], and expanded perlite [2, 19]; natural organic materials, such as sawdusts [20], cotton fibers [21], and rice straws [3, 22]; synthesized polymer materials, such as polystyrene [23, 24], polyurethane sponges [25, 26], polyorganosiloxane [27, 28], melamine-formaldehyde sponges [29, 30], polypropylene nonwoven web [31], and macroporous rubber gels [4, 32]; carbon materials, such as carbon aerogels [11, 33], graphene sponges [10, 34–37], and carbon nanotubes [5, 13, 38]; and hydrophobic bio-based aerogels, such as cellulose aerogels [39–45] and chitin aerogels [46]. By comparison, the absorption capacity (C_{abs}) and buoyancy of inorganic materials are low (< 30 g/g), and their oil/water selectivity and recovery properties are poor [15–17]. Synthetic polymeric absorbents are the most commercially available products for the oil cleanup application due to their inherent oleophilicity. C_{abs} of polymeric materials can be as high as 195 g/g [29]. Still, a major shortage of synthetic materials is well known as slow degradation. Once they are blown away by a gale in practice, new environmental and ecological pressure will be brought [19–47]. Carbonaceous materials have been receiving high attention these days because of their board densities (from 0.16 kg/m^3 to 200 kg/m^3) and high

C_{abs} values (200–600 g/g) [36, 48]. However, the tedious preparation and relatively fragile nature of carbonaceous absorbents retard their scale production.

Based on these facts, bio-based absorbents are more welcome because of their low price, biocompatibility, biodegradability, and sustainability [49]. The adopted bio-based absorbents are kapok fiber [50], sugarcane bagasse [51], rice straw [22], barley straw [52], wood ships [53], etc. These absorbents can be used as received [54], though their C_{abs} are moderate (i.e., 3–50 times of the self-weights) and comparable/lower densities than inorganic and synthetic counterparts [20]. They can also be shaped to pads [55], filters [56], and fibers [57]. A comparison between abovementioned absorbents is listed in Table 2.

Furthermore, to effectively collect oily liquids from water, it is vital to choose a proper format of material as the absorbent. Generally, an ideal absorbent should have the characters of a high sorption capacity, a high oil/water selectivity, a high porosity, a fast oil sorption rate, a high floatability (i.e., hence a low density), low cost, environmentally friendliness, and recyclability [58]. Aerogel is a novel type of porous solid material usually with an extremely low density. Because of its large specific surface area, high porosity, and low density, they are highly promising for rapidly absorbing a large amount of oil from water [59]. And in this area, cellulose, the most abundant biomass on earth with characters of natural renewability, biodegradability, and ease for surface modification, is always the first choice to fabricate bio-sourced aerogel absorbents [41, 43, 45, 60–63]. In this chapter, the preparation, characterization, and properties of the cellulose aerogel absorbents for oil removal in recent years are summarized, and the shortages and possible trends are proposed.

Table 2 Comparison between three kinds of oil absorbents [14] (Copyright © 2017, American Chemical Society)

Classification	Examples	Advantages	Limitations
Inorganic mineral	Zeolites, fly ash, exfoliated graphite, activated carbon, organclay, silica nanoparticles, amorphous silica, silica aerogel	Abundant sources	Difficult recovery, low absorption, eco-unfriendly, low-absorption selectivity and rate, poor biodegradability
Synthetic polymer	Polypropylene fiber cut, polyurethane foams, nanoporous polystyrene fibers, polypropylene nonwoven web, macroporous rubber gels	Moderate absorption capacity, good reusability	Low capacity, poor biodegradability, difficult recovery
Natural organic	Kapok fiber, sugarcane bagasse, cotton, rice straw, cotton, wood chips, barley straw	Abundant resources, low cost, excellent biodegradability, and environmental friendliness	Low capacity, poor hydrophobicity and reusability

2 Raw Materials: Properties and Pretreatments

2.1 Source, Structure, and Properties

Cellulose is the most abundant biopolymer on earth. The study and application of cellulose have been deeply explored and reviewed [64–68]. Cellulose is a linear polymer of glucose with a flat ribbon-like conformation. The repeat unit is comprised of two anhydroglucose rings $(C_6H_{10}O_5)_n$ (n = 10,000 to 15,000, which depends on the cellulose source) through β 1–4 glycosidic bond, i.e., a C1 of one glucose ring is covalently bonded to C4 of the other ring (1 → 4 linkage) by an oxygen [65]. Rich hydrogen bonding between and within the polymer chains stabilizes the linkage and results in the linear configuration. This stable microstructure accumulates to larger fibrils (5–50 nm in diameter and several microns in length). Within these cellulose fibrils, crystalline domains have cellulose chains in order, and amorphous domains have disordered cellulose chains. The microstructure of cellulose is well summarized and can be found elsewhere [69]. Cellulose nanocrystals (CNCs) are extracted from these crystalline regions (Fig. 1).

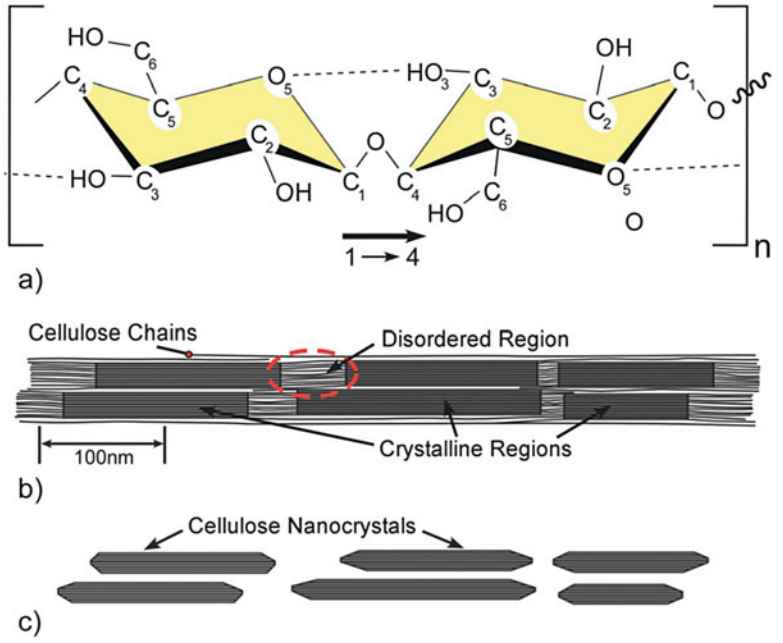

Fig. 1 Schematics of (**a**) single cellulose chain repeat unit, showing the directionality of the 1 → 4 linkage and intrachain hydrogen bonding (*dotted line*), (**b**) idealized cellulose microfibril showing one of the suggested configurations of the crystalline and amorphous regions, and (**c**) cellulose nanocrystals after acid hydrolysis dissolved the disordered regions [67]. (Copyright © 2011, Royal Society of Chemistry)

The sources of cellulose are abundant in nature, which can be extracted from (1) wood, because of the combination of lignin, hemicellulose, and other impurities in which further purification is always needed; (2) plant, such as cotton, ramie, sisal, flax, wheat straw, potato tubers, sugar beet pulp, soybean stock, banana rachis, etc.; (3) tunicate; (4) algae; and (5) bacteria.

2.2 Classification of Cellulose Raw Materials

Raw materials of cellulose can be classified as (1) regenerated cellulose (RC); (2) nanofibrillated cellulose (NFC), in some of the literature it is also written as cellulose nanofibers (CNF) or microfibrillated cellulose (MFC); (3) nanocrystalline cellulose (NCC) or also known as cellulose nanowhiskers (CNW); and (4) bacterial nanocellulose (BC or BNC).

Natural raw cellulose containing lignin, etc. is always colored and stiff. To increase the usability and/or purity of the cellulose, the raw materials require pretreatments. First, dissolving cellulose to obtain regenerated cellulose (RC). However, because of the ultrastrong intermolecular interactions, specific solvents, which are always harmful, are required for the dissolving process. And a subsequent removal of the solvent is probably necessary. Moreover, depending on the location of hydrogen bonds between and within the strands, different crystalline structures of cellulose are classified. Natural cellulose is the type of cellulose I with I_α and I_β structures. BC and algae cellulose is enriched in I_α, while cellulose of higher plants is mainly in I_β. In contrast, cellulose in RC is belonging to cellulose II. This conversion from cellulose I to II is irreversible, suggesting a metastable state of cellulose I and a stable one of cellulose II. The cellulose materials with cellulose I crystalline structure are with higher strength/stiffness and also display larger specific surface than those with cellulose I.

NFCs are isolated from native cellulose fiber suspensions with or without mechanical disintegration [70]. NFC is a long, flexible, and entangled network of cellulose nanofibers (ca. 2–60 nm in diameter and several micrometers in length), in which both individual and aggregated nanofibrils exist with alternating crystalline and amorphous domains [71–73].

NCCs are generated by the removing the amorphous region of partially crystalline cellulose through an acid hydrolysis process. They consist of rod-like cellulose crystals with widths of 5–70 nm and lengths between 100 nm and several micrometers. Comparing with NFC and BC, NCC has a higher crystallinity and a shorter aspect ratio (< 100). Typical characteristics of NFC, NCC, and RC are briefly summarized in Table 3 [70, 71].

Cellulose from bacteria is called bacterial cellulose (BC), a very important kind of cellulose. The chemical structure of BC is exactly the same as plant cellulose. Furthermore, BC presents additional advantages over plant cellulose, including free from other plant components such as hemicelluloses, lignin, and pectin, high crystallinity (70–80%), high water content (to 99%), and relatively high degree of polymerization (up to 8000).

Table 3 Comparative characteristics of three kinds of nanocelluloses [14] (Copyright © 2017, American Chemical Society)

Type	Sources	Preparation methods	Chemical composition	Morphological difference	Dimension size	Crystallinity	Yield	Cost
NFC (MFC, CNF)	Wood, sugar beet, potato tuber, hemp, flax	Delamination of wood pulp by mechanical pressure before and after refining, chemical or enzymatic treatment	Often containing small amount of hemicellulose	Randomly entangled network-like	Diameter, 2–60 nm; length, several micrometers	Relatively low	High	Low
NCC (CNC, CNW)	Wood cotton, hemp, flax, wheat straw, mulberry bark, ramie, Avicel, tunicin, cellulose from algae and bacteria	Acid hydrolysis of cellulose from different sources of cellulose	Almost no hemicellulose	Rigid and rod-like	Diameter, 5–70 nm; length, 100–250 nm (from plant cellulose); 100 nm to several micrometers (from cellulose of tunicate, algae, bacteria)	High	Low	High
BC	Low molecular weight sugars and alcohols	Bacterial synthesis (i.e., *Acetobacter* species)	Pure cellulose without the presence of hemicellulose, pectin, or lignin	Randomly assembled ribbon-shaped fibrils less than 25–100 nm in width	Diameter, 20–100 nm; length, > 100 μm; different types of nanofiber networks	High	Low	High

2.3 Pretreatments of Cellulose

1. **Full dissolution:** Generally, fully dissolving the cellulose in a specific solvent is used to generate RC. Because of the high crystallinity of cellulose, special solvents are required, including heavy metal-amine complexes, mainly copper with ammonia or diamine such as cupric hydroxide in aqueous ammonia (Schweizer's reagent called cuoxam) or cupriethylenediamine (cuen), ammonia or amine/thiocyanate [74], hydrazine/thiocyanate [75], lithium chloride/N,N-dimethylacetamide (LiCl/DMAc) [76, 77], and N-methylmorpholine-N-oxide (NMMO)/water [78]. In the regeneration step, the gelation mechanism bases on the physical crosslinking. In the microstructure, cellulose I crystalline structure is converted to cellulose II type; resulting materials are fragile and have lower aspect ratio of the fibrils with respect to NFC [62, 79]. In addition, the processes of dissolution and probably related gelation and solvent exchange steps are time-consuming when preparing absorbing materials, and used solvents are usually deleterious.
2. **Fibrillation**: Microfibrillation treatment of cellulose fibers through beating or refining is the fundamental procedure to change the fiber morphology in paper-making, in which micro fibrillation is imposing mechanical action of rotating bars to a stationary bedplate on a circulating fiber suspension. During this process, individual fiber is oriented perpendicular to the bars, resulting the release of microfibrils from the compact fiber surface. Because of the rotation intensity, this mechanical treatment can result in hierarchical fibers extending from the surface of the bulk fiber skeleton. To be specific, nanofibrillated cellulose (NFC) is prepared by first preparing an amount of cellulose pulp in deionized water, which is left and swollen at room temperature or a lower one overnight. Subsequently, the suspension is homogenized by a high-shear homogenizer, or a deflaker. Changing the initial cellulose concentration, the shearing rate, and/or homogenization time will lead to different peeling degree of the raw material and surface morphology of resulting fibrils. After this step, centrifugation can be applied to produce a paste-like material with an elevated solid content. By increasing the beating revolution (from 0 to 6000 r), hierarchical fibers on the surface of the main fibrils can be obtained, i.e., increased beating rate will definitely roughen the surface of the fibrils [45].
   The rough morphology of fibrillated cellulose increases the stability in water, especially at low concentrations. This behavior can be explained by the higher hydrophilicity and larger hydrodynamic radius caused by the branched microfibrils on the surfaces.

   The resultant nanocellulose is an attractive material for kinds of practices. The native nanofibrils with a diameter of 3–15 nm can be cleaved from wood pulp by several ways to generate cellulose hydrogels [80–82]. By vacuum drying, freeze-drying, or supercritical CO_2 drying, highly porous nanocellulose aerogels are obtained for further functionalization and utilization [83, 84]. Exploration of fibrillated cellulose effectively avoids the shortages of RC materials.

3. **Chemical treatments:** The sole mechanical disintegration of cellulose fibers requires intensive energy consumption, which could be up to 27,000 kWh per ton of NFC. Therefore, chemical pretreatments are sometime applied to the pulp fibers, acid, enzyme, and/or chemical modifications, for instance. Introduction of charged groups onto the fibers through chemical reactions is able to significantly increase the repulsion between the fibers and promote their individualization. As a result, the energy consumption for the mechanical treatment is largely reduced. The surface functionalized chemicals include carboxymethylation, TEMPO-mediated oxidation, sequential periodate-chlorite oxidation, and trimethylammonium modification [82, 85, 86].

3 Fabrication of the Various Absorbents

The solvent for fully dispersing cellulose is removed to obtain a porous material. Because of the ultralow density and high porosity nature of this material, it is always named as cellulose aerogel. Aerogel is a highly porous material with extremely low densities (0.01–0.4 g/cm^3), high surface areas (30–600 m^2/g), high porosity, and low thermal conductivity [87]. Cellulose-based aerogels were first prepared by Stamm and co-workers [88]. Progresses in this field have been accumulated and accelerated especially after the new century.

Based on the nature of the raw materials, cellulose aerogels include cellulose derivative-based ones [89–91] and regenerated cellulose (RC)-based ones [92–99], which are not strictly nanomaterials. In contrast, the nanocellulose-based ones can be determined as nanomaterials, which have at least one dimension less than 100 nm.

The formation of a 3D interconnected network, or gelation, is critical for preparing a cellulose aerogel. This process of gelation can be classified into physical crosslinking, in which intramolecular and intermolecular multi-hydrogen bonding and entanglement take place [43, 100], and chemical crosslinking, in which additional crosslinking agents are used for more stable chemical bonds between cellulose chains [101, 102]. After proper post-processing for higher hydrophobicity, the aerogel can be used as highly efficient absorbent for oil contaminant removal. In general, there are two critical steps for a molded cellulose network: the first is drying and the second is hydrophobization.

3.1 Drying

The pore structure of cellulose aerogels is susceptible to the drying process because common evaporation of the solvent will generate notable capillary pressure and result in collapsed pores. Therefore, lyophilization and supercritical drying are commonly adopted to avoid the collapse.

3.1.1 Supercritical Drying

Because relatively low pressure and temperature are required during applying, supercritical carbon dioxide (sc-CO_2) is often used for the drying process [87, 89,

90, 103, 104]. A typical supercritical process first requires thorough solvent exchange process, after which, CO_2 flow is pumped into the pot at a medium pressure and temperature [105]. The supercritical temperature (32 °C) and critical pressure (< 8 MPa) for CO_2 are already not harsh; however, it is obvious that this method is rather tedious and time-consuming, making it relatively expensive and dangerous, and thus the consideration in real application increases.

3.1.2 Lyophilization

The conditions for lyophilization or freeze-drying are comparatively gentle. The solvent (water) is first frozen and then sublimated in vacuum. A typical procedure adopts freezing temperature below −20 °C and a subsequent freeze-drying for 3–5 days.

Compared to RC aerogels, NFC aerogels are prepared from the direct drying of frozen aqueous NFC suspensions without complex regeneration steps and harmful solvents, which is therefore more facile and eco-friendly. In addition, the nanocellulose aerogels exhibit superior mechanical integrity after freeze-drying comparing to those of RC aerogels [83].

Furthermore, it is worth mentioning the effect of "ice segregation self-assembly." During the freezing step and the sublimation stages, large ice crystals can cause aggregation of NFC fibrils, which leads to a remarkable decrease of the specific surface [42, 43, 83, 106]. If an extra step of solvent exchange of aqueous NFC suspensions with tert-butanol is used, the abovementioned "ice segregation self-assembly" can be ameliorated [79, 104, 107, 108]. The reason is attributed to the less hydrophilicity of tert-butanol that contributes to a lower extent of surface tension effects during drying. As a result, less significantly aggregated microfibrils and higher specific surface area are obtained [43, 104, 109].

3.2 Hydrophobization

Because of the abundant hydroxyl groups along a hydrocarbon chain, native cellulose aerogels are basically amphiphilic, i.e., being lack of oil/water selectivity. Therefore, increasing oleophilicity in the aerogels will improve the absorbing capability for the oils [37, 43]. This goal can be achieved through introducing surface roughness or using low-surface-energy substances, which includes chemical vapor deposition (CVD), hydrophobic coating in water, atom layer deposition (ALD), cold plasma treatment, sol-gel treatment, and fluorination. And the related agents for hydrophobization are alkoxysilanes, chlorosilanes, TiO_2, SiO_2, alkyl ketene dimer, stearoyl chloride, palmitoyl chloride, (tridecafluoro-1,1,2,2-tetrahydrooctyl) trichlorosilane, and 1H,1H,2H,2H-perfluorode-cyltrichlorosilane. After the hydrophobization reaction, water contact angle (CA) test is the most intuitional method for the surface wettability evaluation. Depending on the values, the surface wettability is classified into hydrophilic ($CA < 90°$), hydrophobic ($90° \leq CA \leq 150°$), or superhydrophobic ($CA > 150°$) [110].

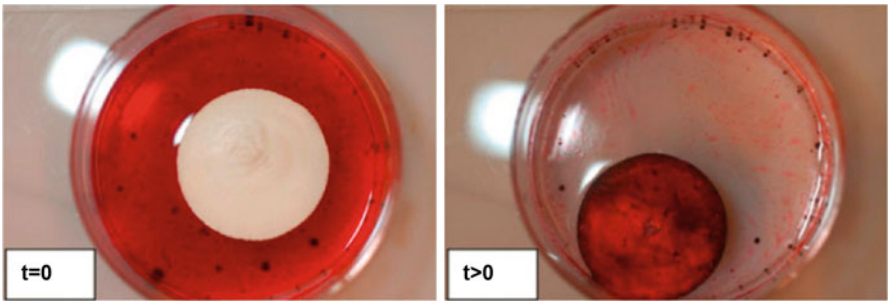

Fig. 2 Treated aerogel is able to float on water and simultaneously absorb a nonpolar liquid (hexadecane, *colored red*) distributed on top of the water phase. The aerogel used in these experiments had been prepared from a 1 wt% NFC dispersion, and it could be removed after the absorption without losing its integrity [111]. (Copyright © 2011, Springer Science+Business Media B.V)

Among these various methods, CVD must be the most adopted one. In the process of CVD, a precursor gas for hydrophobization blows or in situ evaporates in a container, in which the heated sample is to be coated. Subsequently, the chemical reactions of the gaseous agents occur on the sample's surface, which thus results in the formation of a hydrophobic layer. After this reaction, the coated sample may be taken out and placed in a vacuum oven for some time to remove the unreacted agents. For instance, the nanocellulose aerogels prepared by Cervin et al. [111] were hydrophobizated with octyltrichlorosilane (OTCS) by CVD method. The CA value of the final product was ca. 150° (i.e., superhydrophobicity). For example, a hydrophobic aerogel almost absorbs n-hexadecane (oil phase) from water instantly (Fig. 2) with an absorption capacity of 45 times its own weight.

4 Characterization of the Structure and Properties

To full demonstrate the structure and properties of the obtained cellulose absorbents, kinds of characterization should be carried out.

4.1 Structure

4.1.1 Density and Porosity

The basic parameters for a lightweight and porous material are its density and porosity. Bulk density is simply calculated by.

$$\rho_b = \frac{m}{V} \tag{1}$$

where m is the weight, V is the volume, and ρ_b is the bulk density of the absorbent, respectively.

For a cellulose aerogel, or cellulose as the dominant constituent, the skeleton density of material equals to the density of cellulose ($\rho_c = 1.528$ g/cm^3). The porosity (P) of the absorbent is hence calculated by

$$P = \left(1 - \frac{\rho_b}{\rho_c}\right) \times 100\% \tag{2}$$

Wang et al.'s results show that increasing the concentration of cellulose fiber will linearly increase the density and linearly decrease the porosity of the aerogel [45].

4.1.2 Specific Surface Area

The specific surface area was measured by the Brunauer-Emmett-Teller (BET) method, in which a small piece of material is dried under a synthetic gas flow at elevated temperature for some time. The adsorption of N_2 is measured at −196 °C, under a range of relative vapor pressures between 0.05 and 0.2. The specific surface area is evaluated from the obtained adsorption isotherm.

4.1.3 Microstructure

The microstructure of the aerogels is always characterized by scanning electron microscopy (SEM). As expected, an aerogel absorbent displays a porous structure. The differences between these pores are attributed to the used raw materials and preparation conditions. Figure 3 shows the microstructure of a silicon-modified NFC sponge with different Si contents and at different sites, respectively.

Similar results were found by Wang et al. [45], in which the microstructure of cellulose aerogels before and after CVD treatment of MTMS was compared. Before silanization, sponges possessed a continuously three-dimensional (3D) porous structure, formed by randomly entangled cellulose fibers. Hydrophobic modification resulted in a continuous and cloud-like coating of polysiloxane layer, while the porous structure maintains well.

4.1.4 Elemental Distribution

The elemental distribution or mapping can be tested by wavelength-dispersive X-ray spectroscopy (WDX). Zhang et al. used WDX images to visualize the different Si element on the surfaces of the silylated aerogels [42].

4.2 Properties

4.2.1 Surface Hydrophobicity

The surface hydrophobicity or surface wettability of a cellulose absorbent is commonly tested by WCA measurements. WCA is defined as the angle between the tangent line on the droplet which starts from the triple point and the line of the solid surface (Fig. 4a). A water droplet falls directly on a surface of a sample, a photo is recorded by a high-speed camera, and the resulting WCA is calculated subsequently (Fig. 4b).

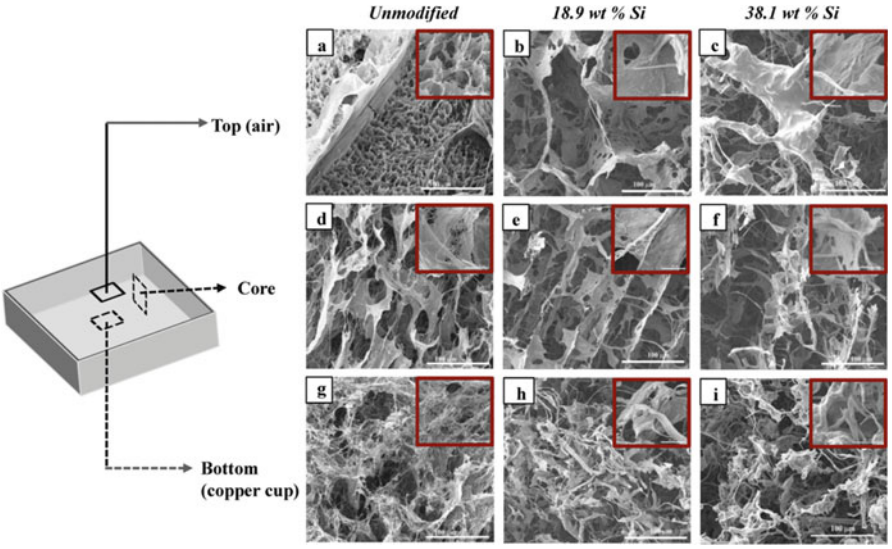

Fig. 3 SEM micrographs of the top (**a-c**), core (**d-f**), and bottom (**g-i**) of NFC sponges with various silicon contents. Two magnifications are shown with scale bars of 100 and 10 μm (inserts) [42]. (Copyright © 2014, American Chemical Society)

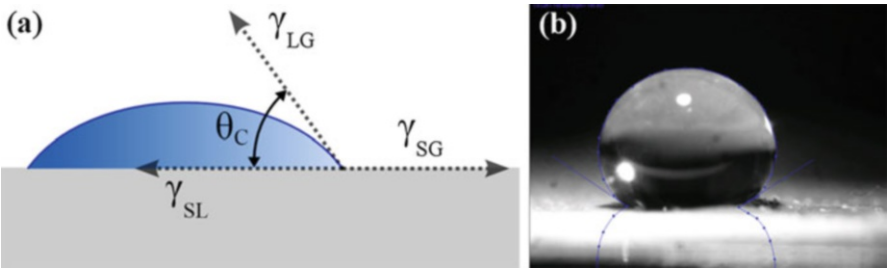

Fig. 4 A scheme for WCA (**a**) and its calculation, (**b**) (Source: https://en.wikipedia.org/wiki/Contact_angle)

For the untreated cellulose absorbents, they displayed a hydrophilic, more precisely, amphiphilic character. Both water and oil droplets can be instantaneously absorbed into these materials with no WCA can be measured on the surfaces, suggesting their poor selectivity for oil and water [112, 113].

The surface after hydrophobization (typically silylation), in contrast, shows WCA in the hydrophobic level. Zhang et al.'s results compared the surface absorption between dodecane, used as model oil and colored red using Sudan III dye, and water, colored blue with Neolan Blau dye. The silylated surface absorbed dodecane instantaneously while water remained, demonstrating its hydrophobicity [42]. In addition, wettability of a material is influenced not only by surface chemistry but also by its morphology and structure [43].

4.2.2 Compressive Properties

An absorbent sample is usually cut into rectangular or cylinder specimens for compression tests. The compression modulus is extracted from the linear part of the stress-strain curve. Figure 5 gives an example of these curves for NFC sponges.

In addition, recovery after compression, i.e., repeated compressibility, is also important for an absorbent. Cellulose is relatively rigid for an absorbing material. A MCF aerogel without sufficient dispersion shows obvious contraction in 10 cycles. In contrast, the aerogel prepared by sufficient dispersion demonstrates good recovery in, for example, 30 cycles [45]. The elasticity of the aerogel will greatly facilitate the oil recovery and reuse of the material.

4.2.3 Oil Absorption

To visualize the absorption capacity of the cellulose-based absorbent, oil that floats on the water and sinks at the water bottom is absorbed by the material. Hydrophobic cellulose aerogels absorb oil swiftly and completely in many established cases, exhibiting good selectivity (Fig. 6). Additionally, the oil-filled aerogels can float on the water surface without oil release, and the absorbed oil can be facilely squeezed out, and an additional hot air drying procedure can be used to remove any residual oil or water.

The absorption capacity (C_{abs}, g/g) of an aerogel is commonly characterized by the ratio between the absorbed oil and the original weight of the material:

$$C_{abs} = \frac{m_1 - m_0}{m_0} \tag{3}$$

where m_0 and m_1 are the weights of the material before and after absorption, respectively. The absorbents have excellent absorption capacity of a wide range of oils and organic solvents, which can be attributed to the high porosity and hydrophobicity of the material. The C_{abs} values locate in the range of 10 to 100 g/g.

In terms of influencing factors on C_{abs}, the density of the oil is critical to the absorption capacity (Fig. 7) because available vacant volume of an absorbent is certain. A highly porous aerogel tends to show high absorption capacity because of its abundant free volume. An oil with low viscosity will also facilitate its penetration into the porous network, which results in a high adsorption capacity. In addition, the capillary effect, van der Waals forces, hydrophobic interaction between the oils and absorbents, morphological parameters, total pore volume, and pore structure of the absorbent also affect C_{abs} value [43, 45, 114, 115].

4.2.4 Reusability

The properties, such as efficiency and cost, of different absorbents are compared and summarized by Wang et al. [45]. From their summary, the methods for oil recovery and absorbent reuse, such as distillation, solvent extraction, and burning, are comparatively complicated, time-consuming, energy consuming, and low efficiency. By comparison, squeezing is the most facile technology. In terms of reusability, the absorbents such as the kapok fiber sponge can be reused by squeezing the absorbed

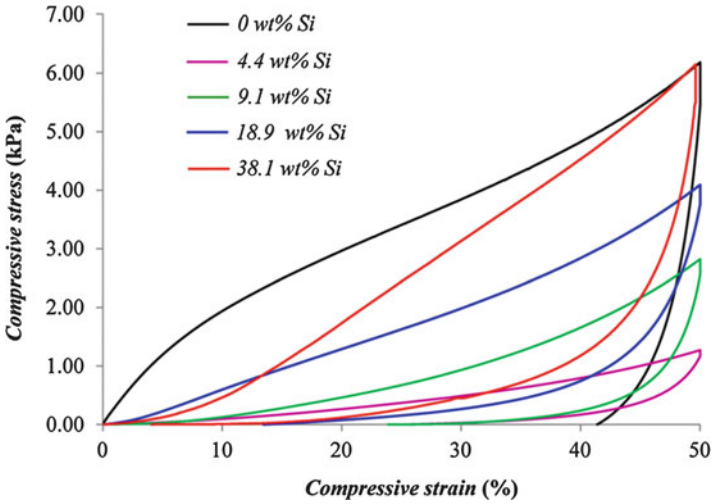

Fig. 5 Compressive stress-strain curves of silylated NFC sponges compressed to 50% strain [42]. (Copyright © 2014, American Chemical Society)

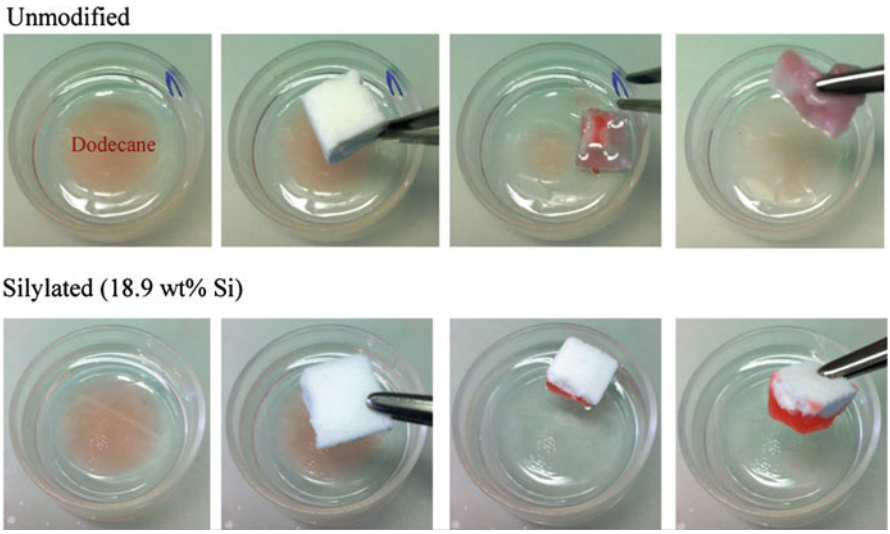

Fig. 6 Removal of a red-colored dodecane spill (0.02 g) from water with the silylated NFC sponge (0.02 g). In comparison, the unmodified material was not selective and lost its original shape [42]. (Copyright © 2014, American Chemical Society)

oil. But their absorption capacities are relatively low. In general, for those carbon absorbents, i.e., carbon nanotube/graphene oxide sponges, carbon nanofiber aerogels from bacterial cellulose, B-doped carbon nanotube sponges, carbon nanotube frameworks, N-doped graphene frameworks, spongy graphene, reduced graphene oxide

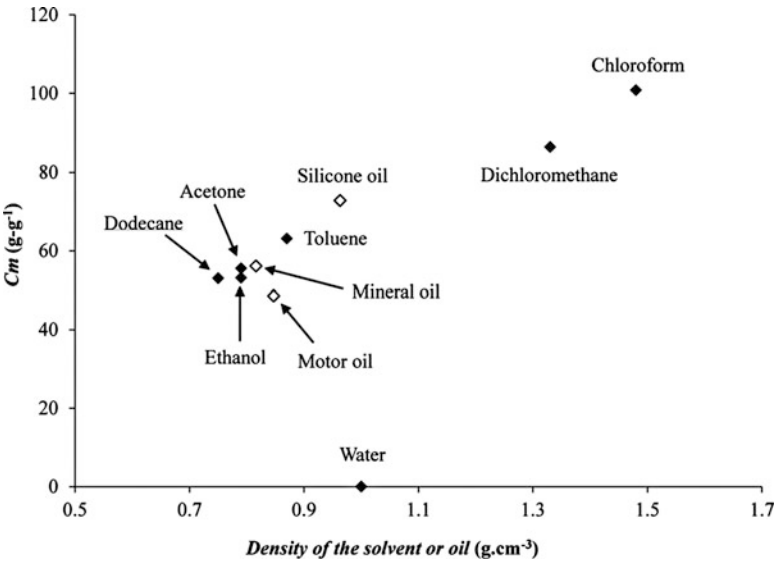

Fig. 7 Absorption capacities of the silylated sponge (18.9 wt% Si), determined for a collection of organic solvents (*filled symbols*) and oils (*empty symbols*). The sample was deposited at the surface of the liquid for 5 s [42]. (Copyright © 2014, American Chemical Society)

foam, and carbon aerogel from winter melon, distillation and combustion are preferred for reusing these materials because of their brittle nature, which are hence less efficient. Although carbon fiber aerogels from raw cotton and waste pulp are reported to be mechanically squeezed to recover oil, their absorption capacity decreased dramatically in just the second cycle (nearly cut in half). Therefore, it is factually improper to adopt mechanical squeezing to recover oil for carbonaceous absorbents.

A simple squeezing can remove most of the absorbed oil, making it possible to reuse both the absorbent and the oil. This merit is very important for practical applications, and therefore its characterization deserves a special attention. Silylated cellulose sponge maintains most of its absorption capacity in 10 cycles [42]. And hydrophobic MCF sponges can maintain more than half of their absorption capacities in 30 cycles [45]. Based on the excellent absorption capacity and recovery property, cellulose absorbents are highly promising in practice.

Despite the obtained high oil absorption capacity, the recovery methods for these cellulose sponges or aerogels still include solvent extraction and distillation at present stage, which are arduous and low-efficient. These shortages are due to the unfavorable shape recovery properties. To overcome the limitations, Wang et al. designed highly elastic oil absorbents based on commercial hardwood pulp. The cellulose fibrils are extracted by beating treatment as papermaking; the resulted 3D network is then freeze-dried and hydrophobizated by CVD treatment [45]. In their results, the microfibrillation degrees of hierarchical fibers can be easily regulated by changing the beating revolutions. Elevated fibrillation degree increases their

recyclability. Recently, Wang et al. designed a gelatin aerogel absorbent with an extremely high reusability [116]. By comparison, cellulose material is relatively brittle and fragile at present stage which requires improvement.

Furthermore, several works report some kinetic models to describe the adsorption behaviors [117–119]. Among these models, the pseudo-first-order and pseudo-second-order models are the most commonly accepted ones for cellulose oil absorbents [13, 120, 121]. The pseudo-first-order model supposes the absorption process controlled by physisorption and described as

$$\ln(q_e - q_t) = \ln q_e - k_1 t \tag{4}$$

whereas the pseudo-second-order model supposes the absorption process controlled by chemisorptions and described as.

$$\frac{t}{q} = \frac{1}{k_2 q_e^2} + \frac{t}{q_e} \tag{5}$$

where q_e and q_t are the adsorption capacities (mg/g) at the equilibrium and time t, respectively. Coefficients of k_1 and k_2 are the rate constants for pseudo-first-order and pseudo-second-order adsorption, respectively. For the hydrophobized cellulose absorbents, the driving forces mainly arise from hydrophobic interactions between the network and oily liquids as well as the capillary effect of the pores [100]. Thus, this adsorption process should be mostly attributed to the physisorption.

5 Cellulose-Related Absorbents and Other Applications

Carbonaceous aerogels or carbon aerogels are intrinsically hydrophobic and widely used as oil absorbent materials. They have excellent advantages of high absorption capacity and chemical and thermal stability. Carbon aerogels are traditionally fabricated through pyrolysis of resorcinol-formaldehyde organic aerogels in an inert atmosphere to form a 3D cross-linked carbonaceous network [122, 123]. The density of the resultant carbon aerogels is always high (100–800 mg/cm^3) [124, 125]. In contrast, their compressive strength is low. By comparison, carbonization of biomass materials is comparatively facile, economic, and with less or no chemical reagents. Therefore, cellulose aerogels can be converted into carbonaceous aerogels via this process. From nature sources, the cellulose aerogels are born with eco-friendliness and sustainability advantages. Furthermore, the carbonaceous aerogels derived from cellulose also have a larger specific surface area, high porosity, and outstanding mechanical properties. Any format of the cellulose aerogel can be used as the precursor of the final product of carbon aerogel. During the procedure of pyrolysis, those hydrophilic functional groups are removed to obtain the oleophilic properties. Wu et al. [12]. first prepared BC pellicles by freeze-drying process, after which carbonaceous materials are obtained by pyrolysis under Ar atmosphere. The resulting 3D interconnected network of carbon aerogel is with a nanofibril

microstructure of 10–20 nm. In addition, this process results in 85% reduction of the volume and also a similarity of the density, which decreases from 9–10 to 4–6 mg/cm^3. The applied temperature in the pyrolysis process is critical for the final carbon aerogels. When this temperature is elevated to ca. 1300 °C, the graphite structures begin to appear. Furthermore, surface wettability is also significantly affected by the pyrolysis temperature. After a pyrolysis at a temperature of 1300 °C, the water contact angle increases from <1° to as high as 128° for the BC aerogels. Furthermore, the resulting carbonaceous aerogels, with a ultralow density (4–6 mg/cm^3) and high porosity (as high as ca. 99.7%), demonstrate excellent flexibility comparing with conventional silica-based aerogels. After the release of a manual compression of more than 90%, its volume reduction can still recover to its original volume.

Carbon aerogels can also be applied in a wide range of organic solvents and oils when they are used as absorbents. Because of the abovementioned porosity and elasticity, the recyclability of these materials is also good. The absorption capacity is as high as 106–212 times of its own weight. For instance, it is 140 g/g for pump oil, 155 g/g for sesame oil, 165 g/g for soybean oil, 170 g/g for diesel oil, and 180 g/g for gasoline, which depends on the density of the oil. There are multiple solutions for recovering the absorbents and/or oil, that is, squeezing, distillation, and direct combustion. Therefore, they are proper for the separation/extraction processes of the pollution caused by organic solvents and oil spilling. NFC aerogel is first cross-linked by a commercial cross-linker, which can be subsequently transferred into carbon aerogel through carbonization process in a N_2 atmosphere [102]. Special attention should be paid to the heating rate; it has a significant impact on the char yield. The density of MFC aerogel decreases from 25 g/cm^3 to only 10 mg/cm^3, whereas the porosity increases from 97.8% to 99% after the pyrolysis process. It is reported that the fiber diameter of the NFC aerogel skeleton dramatically decreases from 50–200 nm to 10–20 nm after the pyrolysis process. In addition, the surface area and the total pore volume of the carbonaceous network dramatically decrease when the temperature increases from 700 °C to 950 °C. And at the higher temperature, a graphite-like structure is also observed. The carbonization process removes the hydrophilic groups and causes high oleophilic property. The carbonaceous aerogel which is pyrolyzed at 700 °C has higher absorption capacity for oils; for instance, this value is 55.8 g/g for pump oil, 72.8 g/g for diesel oil, and 73.6 g/g for canola oil. However, the recycling process (e.g., reusability) is realized by rinsing with alcohol and in 10 cycles [102], which is of relatively low efficiency comparing with squeezing. For clarity, the comparison between different cellulose absorbents is summarized in Table 4.

Additionally, based on their high porosity and extremely large surface areas, a cellulose aerogel without hydrophobization can be also used for water uptaking, dye/pollutants removal, filtration, sound absorption, thermal insulation, catalyst supporter, or precursor of a carbon aerogel. Carbon aerogels attract tense attention as supercapacitors which are promising in energy storage. In addition, a pristine cellulose aerogel can be easily coated by dipping in an electrically conducting polyaniline solution. After rinsing off the unbound conducting polymer and drying,

Table 4 Comparison between various cellulose absorbents [14] (Copyright © 2017, American Chemical Society)

Classification	Cellulose origins	Nanocellulose disintegration	Hydrophobic treatment	Density (mg/cm^3)	Porosity (%)	BET specific area (m^2/g)	Contact angle (°)	Absorption capacity (g/g)	Cost	
									Raw materials	Synthesis methods
NFC-based aerogels	Hardwood Kraft pulp	Mechanical, homogenization	Coated with TiO_2 via ALD	20–30 (before)	> 98 (before)	N.a.	> 90	20–40	–	+
	Sulfite softwood pulp	Carboxymethylation pretreatment, high pressure homogenization	Modified with OTCS via CVD	4–14 (before)	99.1–99.8 (before)	11–42	~150	~45	–	+
	Pine needle cellulose	HCl pretreatment, ultrasonic disintegration	Modified with TMCS via CVD	3.12 (before)	N.a.	20.09 (before)	135	~52	++	+
	Rice straw cellulose	TEMPO oxidation, mechanical disintegration	Modified with OTES via CVD	2.7 (before)	99.5–99.6 (before)	10.9 (before)	N.a.	139–356	++	+
	Hardwood pulp	Mechanical beating	Modified with MTMS via CVD	2.4 (before)	98.4–99.84 (before)	N.a.	> 150	88–228	–	–
	Oat straw cellulose pulp	Mechanical disintegration	Modified with MTMS hydrolyzed polysilane	6.7 (before), 5.07–17.3 (after)	99.6 (before), 99.0–99.7 (after)	24 (before), 3–25 (after)	110–150	49–102	–	–
NFC/PVA hybrid aerogels	Fully bleached eucalyptus Kraft pulp	TEMPO oxidation, mechanical disintegration	Modified with MTCS via CVD	10.6 (before), 13 (after)	> 98	195 (before), 172 (after)	150.3	45–96	–	++

(*continued*)

Table 4 (continued)

Classification	Cellulose origins	Nanocellulose disintegration	Hydrophobic treatment	Density (mg/cm^3)	Porosity (%)	BET specific area (m^2/g)	Contact angle (°)	Absorption capacity (g/g)	Cost	
									Raw materials	Synthesis methods
BC-based aerogel	BC	Commercial BC	Modified with TMCS/TEA in CH_2Cl_2	6.74 (before), 6.69–6.77 (after)	99.6 (after)	160.2 (before), 169.1–180.7 (after)	90	90–185	+	+
	BC/rGO	N.a.	Reduction in H_2 at 200 °C	N.a.	99.84–99.86	N.a.	N.a.	~150	+	+
	BC/SiO_2	Commercial BC	Modified with prehydrolyzed MTMS alcohols	121 (after)	N.a.	507.8 (after)	133	N.a.	+	+
Nanocellulose-derived carbon aerogels	BC pellicles	N.a.	Carbonization under Ar atmosphere	4–6 (before carbonization)	99.7 (before carbonization)	N.a.	113–128	106–212	+	+
	Cellulose microfibrils	Commercial sources	Carbonization under N_2	10 (after carbonization)	99 (after carbonization)	145–521	149	55.8–86.6	–	+

the aerogel becomes an electrically conducting flexible aerogels with a conductivity of 1×10^{-2} S/cm [83].

6 Shortages of Current Cellulose Absorbents

Despite the obtained advantages have proved cellulose an excellent candidate for oil absorbent, there are still some challenges that must be addressed before it becomes predominant in the market.

First, as it is well known, fully isolation and dispersion for cellulose nanofiber preparation require energy input and are still time-consuming. How to increase the efficiency and decrease the expense of this process is very crucial for scale production of cellulose oil absorbents.

Second, cellulose is essentially amphiphilic material which is lake of oil/water selectivity. An additional hydrophobization procedure is necessary, among which the gas-phase deposition, i.e., CVD and ALD, of silanes must be the most adopted modification technology. However, this technology still suffers from the shortage of inhomogeneous silylation with higher modification content on the surface and lower content inside the material. Therefore, designing more effective modification method with time, cost-economic, and eco-friendly properties for this goal is thus always a challenge for academic and industrial researchers.

Third, recovery methods of distillation, rinsing, vacuum distillation, and burning are more complicated and lower efficient than simple squeezing. After squeezing, both the absorbent and the oil are recovered and reused. However, the skeleton of a cellulosic porous material has relatively low flexibility, which limits its reusability. After times of compression-absorption cycles, cellulose absorbents tend to exhibit a decrease in their absorption capacity.

7 Conclusion and Future Scope

In this chapter, the methods to design cellulose absorbents and the characteristics and properties of the resulting materials have been summarized. Cellulose has the advantage of abundance, and the processing of cellulose raw materials becomes easier, cheaper, and more efficient. More cellulose absorbents will be explored in the future. We expect possible trends in this field as following; first, the concept of sustainability is increasingly and widely accepted; the absorbents from recycling of waste cellulose will be increased. And second, hybrid materials with cellulose as one component will show collaborative advantage from each component of this material.

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Cellulose-Based Hydrogels as Smart Corrosion Inhibitors

31

Reem K. Farag and Ahmed A. Farag

Contents

Abstract

This chapter describes briefly the cellulose-based hydrogel definition, classifications, cross-linked structure of hydrogels and types of polymers used in tailor-made hydrogel. In addition, it describes a brief overview of hydrogel-based on cellulose, definitions, methods of preparation, and applications as smart corrosion inhibitors as discussed in some detailed in the text. Finally, this study provides us the use of polymeric hydrogels as corrosion inhibitors. Corrosion problems have driven out to be progressively serious and reached out to different fields. However, corrosion inhibitors are usually not satisfactory due to bad performance during the mixing process, hydrolyze weather, and decompose during working

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process. These problems settled by solid corrosion inhibitor, which will release under control. Hydrogel can have the capacity to hold many liquids and characterized by a soft rubbery consistency like living tissues, making them a perfect substance for a variety of applications. In this manner, hydrogels utilized as smart carriers for controlled release of corrosion inhibitors.

Keywords
Hydrogel · Cellulose · Metal substrates · Corrosion inhibitors · Release process · pH sensitivity

1 Hydrogels: A Brief Overview

Hydrogels are polymeric three-dimensional networks capable of absorbing high amounts of water or biological fluids [1]. Their affinity to absorb water attributed to the presence of hydrophilic groups such as –OH, –CONH–, –$CONH_2$–, and –SO3H in polymers forming hydrogel structures [2]. Accordingly, Table 1 represents hydrophilic polymers forming hydrogel structure. Due to the contribution of these groups and domains in the network, the polymer is thus hydrated to different degrees

Table 1 Hydrophilic polymers used in preparation of hydrogels

1. Natural polymers and their derivatives
• Anionic polymers**: HA, alginic acid, pectin, carrageenan, chondroitin sulfate, dextran sulfate**
• Cationic polymers**: chitosan, polylysine**
• Amphipathic polymers**: collagen (and gelatin), carboxymethyl chitin, fibrin, and carboxymethyl cellulose**
• Neutral polymers**: dextran, agarose, pullulan**
2. Synthetic polymers
• Polyesters**: PEG –PLA – PEG, PEG –PLGA–PEG, PEG –PCL – PEG, PLA – PEG –PLA, PHB, P(PF-co- EG)6acrylate end groups, P(PEG/PBO terephthalate)**
• Other polymers**: PEG-bis-(PLA-acrylate), PEG6CDs, PEG-g-P(AAm-co-Vamine), PAAm, P (NIPAAm-co-AAc), P(NIPAAm-co-EMA), PVAc/PVA, PNVP, P(MMA-co-HEMA), P(AN-co- allyl sulfonate), P(biscarboxy-phenoxy-phosphazene), P(GEMA-s ulfate)**
3. Combinations of natural and synthetic polymers
• **P(PEG-co-peptides), alginate-g-(PEO– PPO– PEO), P(PLGA-co-serine), collagen-acrylate, alginate-acrylate, P(HPM A-g-peptide), P(HEMA/Matrigel®), HA -g-NIPAAm**

Abbreviations: *HA* hyaluronic acid, *PEG* poly (ethylene glycol), *PLA* poly(lactic acid), *PLGA* poly (lactic-co-glycolic acid), *PCL* polycaprolactone, *PHB* poly(hydroxy butyrate), *PF* propylene fumarate, *EG* ethylene glycol, *PBO* poly(butylene oxide), *CD* cyclodextrin, *PAAm* polyacrylamide, *PNIPAAm* poly(N-isopropyl acrylamide), *PVA* poly(vinyl alcohol), *PVamine* poly(vinyl amine), *PVAc* poly(vinyl acetate), *PNVP* poly (N-vinyl pyrrolidone), *PAAc* poly(acrylic acid), *HEMA* hydroxyethyl methacrylate, *PAN* polyacrylonitrile, *PGEMA* poly(glucosylethyl methacrylate), *PEO* poly(ethylene oxide), *PPO* poly(propylene oxide), *PHPMA* poly(hydroxypropyl methacrylamide), *PEMA* poly(ethyl methacrylate), *PAN* polyacrylonitrile, *PMMA* poly(methyl methacrylate)

(sometimes, more than 90%wt.), depending on the nature of the aqueous environment and polymer composition [3, 4]. In contrast, polymeric networks of hydrophobic characteristics (e.g., poly (lactic acid) (PLA) or poly (lactide-co-glycolide) (PLGA)) have limited water-absorbing capacities (<5–10%). While the water content of a hydrogel determines its unique physicochemical characteristics, these structures have some common physical properties resembling that of the living tissues than any other class of synthetic biomaterials, which attributed to their high water content, their soft and robbery consistency, and low interfacial tension with water or biological fluids [5]. Despite their high water-absorbing affinity, hydrogels show a swelling behavior instead of dissolved in the aqueous surrounding environment because of the critical cross-links present in the hydrogel structure. These cross-links are from two main categories including: (i) physical (entanglements or crystallites) and (ii) chemical (tie-points and junctions) [6]. The cross-links between polymer chains network are provided by covalent bonds, hydrogen binding, van der Waals interactions, or physical entanglements [7].

1.1 Classification and Basic Structure of Hydrogel

To achieve a hydrogel system with predetermined and well-defined physicochemical parameters and release profiles, knowledge of polymer network synthesis and chemistry, quantitative and novelistic features of materials, interaction parameters, and disintegration/release kinetic and transport phenomena seems to be playing fundamentally important roles. In a general view, hydrogels can be classified based on a variety of characteristics, including the nature of side groups (neutral or ionic), mechanical and structural features (affine or phantom), method of preparation (homo- or copolymer), physical structure (amorphous, semicrystalline, hydrogen bonded, supermolecular, and hydrocolloidal), and responsiveness to physiologic environment stimuli (pH, ionic strength, temperature, electromagnetic radiation, etc.) [8, 9]. The polymers commonly used in preparation of hydrogels with pharmaceutical and biological applications are from natural or synthetic origins [10]. Typical examples of natural, synthetic, and combinational, i.e., semisynthetic polymers used in hydrogel preparations are summarized in Table 1. Hydrogels have various advantageous properties such as being usually nontoxic, biocompatibility, and showing a number of remarkable physicochemical properties that make them suitable for different applications in drug delivery systems. In comparison, the well-defined structure of synthetic polymers may lead to hydrogels with well-defined and fine-tunable degradation kinetic as well as mechanical properties. As mentioned, water content plays an important role in determining the overall characteristic of a polymeric network. Accordingly, hydrophilic hydrogels with high amounts of water in their structures show distinctive properties compared to hydrophobic polymeric networks. Furthermore, hydrogels have significantly milder conditions for preparation with gel formation occurring at ambient temperatures, and organic solvents are rarely required. Moreover, the characteristics and potential applications of hydrogels of

Table 2 Monomers commonly used in synthesis of synthetic hydrogels for pharmaceutical application

Monomer chemical name	Monomer abbreviation
Hydroxyethyl methacrylate	**HEMA**
Hydroxyethoxyethyl methacrylate	**HEEMA**
Hydroxydiethoxyethyl methacrylate	**HDEEMA**
Methoxyethyl methacrylate	**MEMA**
Methoxyethoxyethyl methacrylate	**MEEMA**
Methoxydiethoxyethyl methacrylate	**MDEEMA**
Ethylene glycol dimethacrylate	**EGDMA**
N-vinyl-2-pyrrolidone	**NVP**
N-isopropyl acrylamide	**NIPAAm**
Vinyl acetate	**VAc**
Acrylic acid	**AA**
Methacrylic acid	**MAA**
N-(2-hydroxypropyl) methacrylamide	**HPMA**
Ethylene glycol	**EG**
PEG acrylate	**PEGA**
PEG methacrylate	**PEGMA**
PEG diacrylate	**PEGDA**
PEG dimethacrylate	**PEGDMA**

different structures rely not only on the preparation methods but also on the monomers used in the synthesis of hydrogel polymeric networks. A summary of monomers most commonly is used in the fabrication of hydrogel structures of pharmaceutical interest as shown in Table 2. Hydrogels, particularly those intended for applications in drug delivery and biomedical purposes, are required to have acceptable biodegradability and biocompatibility that necessitates the development of novel synthesis and cross-linking methods to design the desired products. In this way, a great variety of cross-linking approaches developed to prepare desired hydrogels for each particular application [11]. These cross-linking methods used for preparation of hydrogels listed in Fig. 1.

Structural evaluation of hydrogels reveals that ideal networks rarely observed. Figure 2a shows an ideal macromolecular network (hydrogel) indicating tetra-functional cross-links (junctions) produced by covalent bonds, where Mc is the average molecular weight between cross-links. However, the possibility exists of multifunctional junctions (Fig. 2b) or physical molecular entanglements (Fig. 2c) playing the role of semipermanent junctions. Hydrogels with molecular defects are always possible. Figure 2d and e indicate two such defects, unreacted functionality (Fig. 2d), and/or chain loops (Fig. 2e). Neither of these defects contribute to the mechanical or physical properties of a polymer network. The term junction or cross-link (a filled circle symbol in Fig. 2) indicates the connection point of several chains. This junction may be ideally a carbon atom, but it is usually a small chemical bridge (e.g., an acetal bridge in the case of poly(vinyl alcohol)) of molecular weight much smaller than that of the cross-linked polymer chains. In other situations, ajunction may be a bulky structure of fused aromatic rings, as in the macromolecular network structure of coal. On the other hand, an

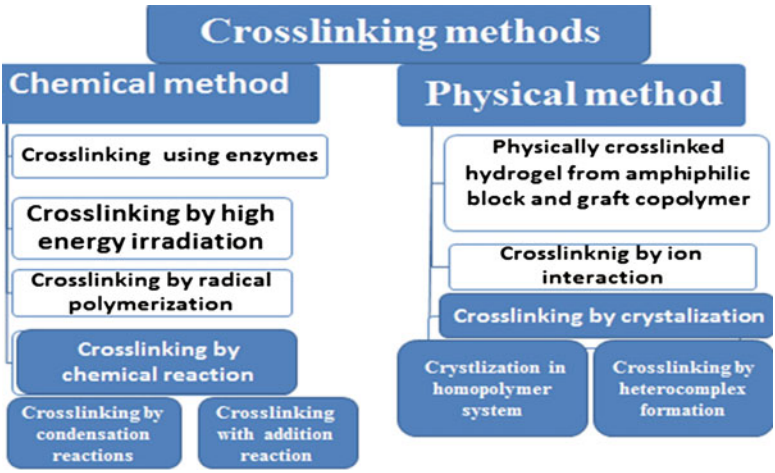

Fig. 1 Cross-linking methods for hydrogel preparation

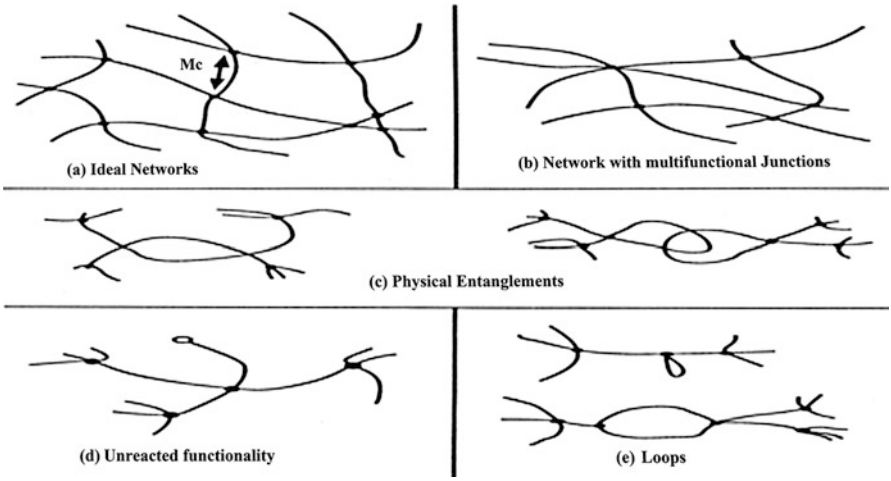

Fig. 2 Network structure in hydrogel

association of macromolecular chains due to van der waals forces, as in the case of the glycoprotein network structure of natural mucus, or an aggregate formed by hydrogen bonds, as in caws of aged microgels formed in polymer solutions. Finally, the structure may include effective junction, which can be either simple, physical entanglements of permanent or semipermanent nature, or ordered chains forming crystallites. Thus, the junctions should never consider as a "volumeless point." The usual depiction is applied when developing structural models for analysis of the cross-linked structure of hydrogels.

2 Cellulose-Based Hydrogels

Hydrogels is divided into two categories, according to their natural or synthetic origin: biopolymer-based or synthetic. Considering the biocompatibility, biodegradability, and tissue-mimicking consistency of biopolymer-based hydrogels, they have acquired increasing attention. Among the biopolymers, cellulose and chitin are two of the most abundant on earth, thus having great potential in hydrogel preparation. Cellulose consists of a straight chain of β-(1 → 4)-linked D-glucose units, and chitin, structurally similar to cellulose, is a long-chain copolymer of β-(1 → 4)-linked 2-acetamido-2-deoxy-β-D-glucose units, with acetamide groups in the C-2 position. If the degree of acetylation (%DA) of the biopolymer is lower than 50%, it is no longer called chitin but chitosan. The plentiful hydrophilic functional groups (hydroxyl and/or amino) in the backbones of either cellulose or chitin qualify them as promising materials for highly absorbent hydrogel systems.

Traditional hydrogels are absorbent but maintain poor physical and mechanical properties and limited functionalities. There has been an increased effort to enhance these physical properties and functionalities by incorporating filler particles as physical cross linkers into the hydrogel network. Such filler would enhance the properties and applicability of the hydrogel [12–14]. Hydrogel based on cellulosic compounds is the most abundant one. However, the strong intermolecular and intramolecular hydrogen bonds between the hydroxyl groups along the chain backbone not only limit the water solubility but also lead to the poor reactivity of cellulose [15]. In spite of the superiority of carboxymethyl cellulose (CMC) over other natural polymers, its biodegradability limits its uses considerably. To overcome this problem, grafting of copolymer on to polymeric backbone of carboxymethyl cellulose improves its applicability and modifies its properties such as swelling and flocculation [16–18].

Farag et al. [19] prepared hydrogel nanoparticles and applied for copper and lead ion removal. This is achieved by graft copolymerization of acrylic acid (AA) and N-isopropylacrylamide (NIPA) along the chains of carboxymethyl cellulose substrate using inverse microemulsion method. Furthermore, the pH-responsive behavior of the prepared grafted nanogels is studied at wide pH range to investigate the efficiency of these nanogels under drastic conditions and in high alkaline and high acidic media.

Hydrogels Based cellulose is very interesting materials since they find application in many fields [20] (agriculture, tissue engineering, drug delivery, biosensors, coatings, corrosion inhibitors etc.) with the advantage of being prepared starting from environmentally friendly, renewable, and low cost raw materials. Among polysaccharides, cellulose is the most abundant one and available worldwide, and it combines hydrophilicity with good mechanical properties. Both of these competitive characteristics are due to the numerous hydroxyl groups that interact by hydrogen bonds preferentially with water (amorphous domains) or with hydroxyl groups of adjacent polymer chains (crystalline domains). The complex system of hydrogen bonds between hydroxyl groups (supramolecular structure) contributes to both cellulose's mechanical strength and its insolubility in water and in the major

part of solvents [21]. Intense research has focused on the dissolution of cellulose that is providing continuous improvements of efficiency in solvents such as NaOH/urea aqueous solutions and similar systems (i.e., NaOH/urea/thiourea, NaOH/polyethylene glycol, LiOH/urea) [22–31], which are non-reprivatizing, inexpensive, and nontoxic cellulose solvents. The effort for systematic research is difficult by the variability of cellulose, whose characteristics change with its source and batches. Therefore, solubilization parameters have to be adjusted depending on the particular type of cellulose. In the literature, characterizations of many kinds of hydrogels prepared from different types of cellulose, alone or mixed with its derivatives, such as lignin, chitin, or polyvinyl alcohol, are reported. The synthesis of cellulose-based hydrogels generally consists of two steps [32–38]: (i) solubilization of cellulose fibers or powder and (ii) chemical and/or physical cross-linking, in order to obtain a three-dimensional network of hydrophilic polymer chains, which is able to absorb and retain a significant amount of water. By tuning the cross-linker and cellulose concentrations, it is possible to optimize the hydrogel mechanical properties and swelling capabilities. Thanks to these recent developments and due to the growing importance of green chemistry, versatile materials derived from cellulose, such as hydrogels and aerogels, have raised renewed interest in the field of electrochemical devices involving energy generation and storage [39, 40].

2.1 Synthesis of Cellulose-Based Hydrogels

Most hydrogels based on native cellulose are usually prepared through a two-step process involving dissolution followed by cross-linking (i.e., gelation).

2.1.1 Dissolution of Cellulose-Based Hydrogels

Specific solvent methods are required to dissolve native cellulose, which possess poor solubility characteristic owing to the various inter- and intramolecular hydrogen bonds between polymeric chains. Limited solvents have been used for the suspension of natural cellulose. These contain some predictable polar solvent systems such as N-methylmorpholine oxide (NMMO), lithium chloride/dimethylacetamide (LiCl/DMAc), paraformaldehyde/dimethylsulfoxide (PF/DMSO), triethylammonium chloride/dimethylsulfoxide (TEAC/DMSO), tetrabutylammonium fluoride/dimethylsulfoxide (TBAF/DMSO), lithium chloride/N-methyl-2-pyrolidone (LiCl/NMP), and calcium chloride dihydrate/methanol ($CaCl_2{\cdot}2H_2O$/MeOH). Although the use of these polar solvents has somewhat alleviated the issues with the biopolymer's intractability, the toxicity or corrosively of these organic components can inhibit batch fabrication and prospective applications of the prepared gels. Another latest possibility for cellulose dissolution and hydrogel fabrication includes ionic liquids (ILs), deep eutectic solvents (DESs), and alkali or alkali/(thio)urea aqueous systems developed since the 2000s. Various ILs used for cellulose dissolution consist of an imidazolium, pyridinium, ammonium, or phosphonium cation paired with a strongly basic, hydrogen bond accepting anion (e.g., OAc^-, $HCOO^-$, $HSCH_2COO^-$, $(MeO)HPO_2^-$, $(MeO)MePO_2^-$, $(MeO)2PO_2^-$, Cl^-, or Br^-).

And several of these ILs including 1-ethyl-3-methylimidazolium acetate ([C2mim][OAc]), 1-butyl-3-methylimidazolium chloride ([C4mim]Cl), and 1-allyl-3-methylimidazolium chloride ([Amim]Cl) have been applied in the preparation of cellulose gels. In contrast to the enormous attention captured by cellulose, not much information is yet available on chitin-dissolving ILs; typical ILs in this context are 1-allyl-3-methylimidazolium bromide ([Amim]Br), [C2mim][OAc] and 1-butyl-3-methylimidazolium acetate ([C4mim][OAc]). Deep eutectic solvents (DESs) are fluids obtained by heating two or three components that are capable of self-association through hydrogen bonding. DESs have the same physicochemical behaviors to those of ILs except that they do not entirely consist of ionic species and may be cheaper. The classic examples are the combinations of choline chloride (mp 302 °C) with urea (mp 133 °C) or thiourea (mp 175 °C), forming a DES with a mp of 12 °C or 69 °C, respectively. Dissolution of cellulose in DESs is verified. The mechanism of the dissolution of cellulose in all these solvents has not fully determined yet. The widely accepted opinion is that hydrogen bond acceptors (N–O, Cl^-, OAc^-, etc.) and/or donors (–NH_2 in urea or thiourea) of the solvent break up the intra- and intermolecular hydrogen bonds in the biopolymer chains upon stirring, heating, or low temperature treatment [41, 42].

2.1.2 Cross-Linking of Hydrogels Based on Cellulose

Physical Cross-Linked Hydrogels Based on Cellulose

Physical hydrogels are cross-linked by physical interactions such as chain entanglements, van der Waals forces, and hydrogen bonds, hydrophobic or electronic associations. For cellulose physical hydrogels have been prepared from four major biopolymer sources: natural cellulose dissolved in definite solvents, nanowhiskers (dispersed in water), biopolymer derivatives (dissolved in water or acid), and bacterial cellulose (BC; dissolved in definite solvents or biosynthesized directly into gels during bacterial nation). Cellulose-based polymers dissolved in solution behave as random coils, semiflexible (or semirigid) chains, or entangled chains, and the degree of entanglement depends on the polymer concentration. While polymer solutions of low concentrations are completely isotropic, with increasing polymer concentration, the transition from solution to a liquid crystalline gel takes place followed by gelation into a solid gel that has an anisotropic structure. The gel structure becomes more and more organized and stable as biopolymer concentration increases due to the higher degree of entanglements and the more hydrogen bonding interactions that exist. Further, upon curing (i.e., keeping the solution at various temperatures between 5 and 60 °C for minutes or weeks) or coagulation (i.e., immersion in certain non-solvents such as water, ethanol, methanol, H_2SO_4/Na_2SO_4, etc.) in various fashions (e.g., beading, molding, or casting; the physicochemical interactions between the polymer chains increases and the stability of the hydrogel enhances). Usually, physical associations are reversible, leading to a thermo-reversible and "green" (without cross-linkers) sol-gel transition process. However, if (a) the reversible gel is coagulated in an anti-solvent, or (b) the NaOH/urea (or thiourea) solvent denatures at high curing temperatures (>60 °C, resulting in a yellow color) via reaction and thermal decomposition of the solvent

molecules, the solvents are washed out (in "a") or destroyed (in "b"), resulting in formation of the so-called irreversible gels. Such irreversible physical gels, when vacuum or super critically dried, exhibit lower degrees of crystallinity (reduced by 9–22%) than natural cellulose. In addition, cellulose (I) changes to cellulose (II) after dissolution and gelation [43, 44].

Chemical Cross-Linked Hydrogels Based on Cellulose

With the formation of a covalently bound 3D hydrophilic cellulose-based hydrogels, network is achieved through the use of chemical cross-linkers during gelation, i.e., small bifunctional or multifunctional molecules such as 1,2,3,4-butanetetracarboxylic dianhydride (BTCA), succinic anhydride (SA), citric acid (CA), epichlorohydrin (ECH), ethylene glycol diglycidyl ether (EGDE), and divinyl sulfone (DVS). Chemical cross-linkers form covalent bonds that link one polymer chain to another. According to the mechanism of cross-linking reactions, chemical cross-linkers for cellulose can classify into two types: (a) esterifying agents including carboxylic acids and carboxylic anhydrides and (b) etherifying agents including organochlorine, epoxide, and vinyl compounds. The first type of cross-linkers results in formation of –COOR bonds and probably a few peptide bonds (–CONH–) in chitin gels, while the second type of cross-linkers results in formation of R–O–R bonds [45, 46].

Irradiative Cross-Linked Hydrogels Based on Cellulose

Irradiation is a useful method for the formation of covalent bonding between polymer chains. This method is advantageous because of the high purity of the hydrogel formed without use of toxic cross-linkers, thus increasing the applications in food and pharmaceutical industries. However, merely a small portion (17–30%) of gel aggregates could be obtained by γ-ray irradiation at a dose of 20 kGy from 20 wt% biopolymer solutions (such as cellulose/IL/water, CMC, and carboxymethyl chitosan (CMCts) aqueous solutions), with the assist of created hydroxyl radicals. Electron beam (EB) irradiation in vacuum seems to be able to increase the gel yield. After EB irradiation, the gel fraction reached up to 55% at 20 kGy. Additionally, instead of low income and a liquid creation, Petrov et al. [47] obtained opaque spongy materials via UV irradiation from moderately frozen semi-dilute (3 wt%) aqueous polymer (e.g., HPMC, HEC, and MC) solutions with (4-benzoylbenzyl) trimethylammonium chloride (BBTMAC) as a photoinitiator. It suggested that after freezing, the photoinitiator and water molecules connected to the polymer through hydrogen bonds could form a nonfrozen liquid microphase in which the polymer concentration was very high, resulting in a sufficient number of chains in close enough vicinity to bind with each other during irradiation. Additionally, a "radical cross-linker" (usually N,N′-methylenebisacrylamide (MBAAm)) could be added to the solution before irradiation to improve the gelation effectiveness. It has been reported that macroradicals emerge preferentially in weakened 1 and 4 positions of cellulose as a result of the fracture of C–H bonds upon irradiation, while macroradicals of the derivatives are created in the side chains during radical cross-linking. Degradation of the polymer chains participates with cross-linking during irradiation,

especially at high-energy doses and low polymer concentrations (10 wt%), resulting in the destruction of network structure and decrease of tensile strength. Degradation can decline by (a) much higher radical amount created in the system under using electron beam irradiation instead of γ-irradiation or by (b) irradiation in an oxygen-free atmosphere to elude the production of peroxides and oxides [48].

3 Smart Cellulose-Based Hydrogels Behavior

Cellulose can used to fabricate smart polymers, which present intelligent manners under environmental stimulus. Smart material is defined as one in which a key material property could be altered in a controlled manner in response to the introduction of a predetermined external stimulus [49]. These stimuli-responsive materials might develop to undergo such variations as specimen shape, mechanical rigidity/flexibility, opacity, and porosity. Due to the interesting property changes, smart materials have great prospective in several applications. Smart hydrogel-based cellulose undergoes swelling and deswelling in response to environmental changes and thus can be useful as super absorbent hydrogels for various applications. Stimuli-responsive hydrogel-based cellulose grafted membranes can regulate their pore sizes through polymer swelling and shrinking in response to stimulus. This membrane is fabricated to use for separation membranes and sensors. The stimuli can form by variations of pH, temperature, ionic concentration, etc. Smart polymers based on cellulose acquire its sole behaviors, for instance, strong mechanical strength, and biocompatibility; thus, researches on cellulose-based smart polymers have flowered throughout the latter dated.

Smart polymers based on cellulose fabricate through chemical modifications or physical incorporating/blending (Fig. 3) as described previously. Chemical modifications can be formed in both homogeneous and in heterogeneous surroundings. In the processes of incorporating/blending (physical modification), cellulose or cellulose derivatives act as matrices, fillers, or coatings/shells. The prepared smart

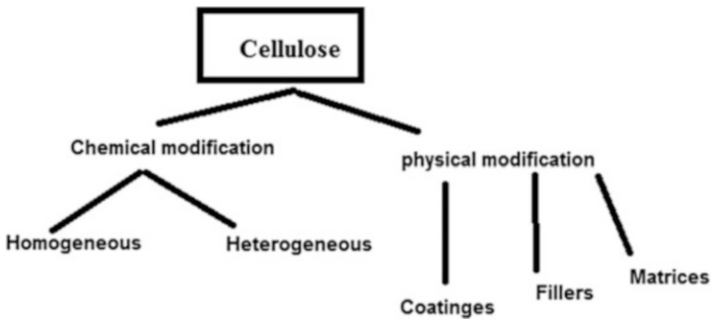

Fig. 3 Preparation of cellulose-based smart materials

polymer-based cellulose is usually in the forms of copolymers, aggregates, particles, gels, fibers, membranes, and films.

Cellulose has three alcoholic hydroxyl groups in each chain, and chemical modifications can performed on these hydroxyls with practical relevance. The primary hydroxyl group at C-6 and the two secondary ones at C-2 and C-3 can participate in all the classical reactions as the alcoholic hydroxyl group does, including esterification, etherification, and oxidation reactions. Chemical modifications can be conducted both in heterogeneous and homogeneous conditions. Due to the high crystallinity, cellulose can only be dissolved in limited solvents, so many modifications are conducted in heterogeneous conditions. Since chemical reactions occur only at the surface layer in heterogeneous conditions, the gross structure of the cellulose sample is largely maintained. In homogeneous conditions, the original supermolecular structure of the sample is destroyed and the limitation of the completeness of the chemical reaction minimized; thus, well-defined cellulose materials are obtained through chemical modifications in homogeneous conditions.

Smart materials based on cellulose are usually made of hydroxypropyl cellulose HPC and carboxymethyl cellulose (CMC), not only because of the water solubility of these derivatives but also because of the temperature-responsive properties of HPC and pH-responsive properties of CMC. These hydrogels possessed temperature- or pH-responsive characteristics as their cellulose ingredients [50]. Apart from that, these hydrogels were salt-responsive in aqueous media. The higher the concentration, and the higher the chelating ability of the salts, the less water the hydrogels could uptake. The increase in the ionic strength reduced the difference in the concentration of movable ions between the polymer matrix and the external solution and led to an immediate contraction of gel. The decreasing was more significant to ions with higher valence, like Ca^{2+}, Mg^{2+}, and Al^{3+}, arising from the complex formation ability of the hydrophilic groups, including intramolecular and intermolecular complex formations, or because one multivalent ion was able to neutralize several charges inside the hydrogels [51]. Salmawi and Ibrahim reported that clay mixed with CMC reduced the water uptake capacity of the prepared hydrogels [52], while another research group reported that the water uptake capacity improved by adding a suitable amount of rectorite, yet excessive rectorite induced the reduction in water absorption. The superabsorbent nanocomposites based on CMC and rectorite also showed saline, pH, and organic solvent responsive. Using CNC to prepare "smart" hydrogels could not only improve the swell capacity but also improve the mechanical strength of the hydrogels [53]. Farag et al. [19] investigated the pH-responsive behavior of graft copolymerization of acrylic acid (AA), and N-isopropylacrylamide (NIPA) along the chains of carboxymethyl cellulose substrate was investigated in pH range 2–12 and expressed in terms of their swelling behavior. It noted that the swelling capacity increased with an increase in pH up to 12. Increasing the pH of the solution increases the ion dissociations of COOH, and, consequently, the charges on the polymeric chains increase [54]. The pH sensitivity of CMC4-g-p(NIPAco- AAC) as representative sample is shown in Fig. 4. It is obvious that the swelling increases with increasing pH from 2 to 12 reaching maximum swelling degree ranging from 90 to 100.

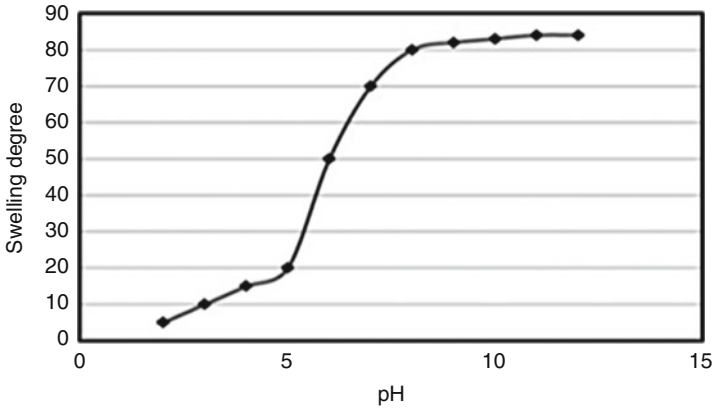

Fig. 4 Effect of pH value on swelling behavior of CMC4g(NIPA-CO-AAc) cross-linked by 1% EGDMA

3.1 Swelling Behaviors for Smart Cellulose-Based Hydrogels

To study the swelling behavior for cellulose-based hydrogel in water and at different pH, some swelling and network parameters characteristics of the cross-linked polymers should be investigated. Hydrogels are kept in 20 mL distillated water, 20 mL buffer solution of pH 1.2, or 20 mL buffer solution of 7.4 at room temperature (25 °C) for 72 h to reach swelling equilibrium. At predetermined moments, hydrogels are removed from solutions, wiped with filter paper, and then weighed. The swelling and network properties of the absorbent hydrogel are studied as follows.

3.1.1 Swelling Kinetic Parameters

Water absorbency in gg^{-1} and equilibrium water content (EWC) are determined according to Eqs. (1 and 2).

$$\mathrm{Q\ (g/g)} = \begin{array}{l}(\text{weight of absorbed water in sample}) \\ /(\text{weight of sample before water absorbency})\end{array} \tag{1}$$

$$\mathrm{EWC\%} = ((\text{wt of gel} - \text{wt.of xergel})/\text{wt.of gel}) \times 100 \tag{2}$$

Swelling kinetics of the prepared cross-linked copolymers were determined according our previous work [55], in which the swelling rate can be described by the following experimental equation:

$$\ln(Q_{max}/(Q_{max} - Q)) = kt \tag{3}$$

where Q_{max} and Q are the maximum and the characteristic water absorbency, respectively, while K is the swelling kinetic constant.

The characteristic swelling time is defined at

$$Q = 0.632\ Q_{max} \tag{4}$$

3.1.2 Network Parameters

Network parameters of cross-linked polymers including theoretical cross-link density νt, Flory-Huggins-type interaction parameter χ, effective cross-link density νe, molar mass between cross-links (Mc) and modulus of elasticity (GT) were calculated according Flory [3] swelling mode. Theoretical cross-link density ν_t has been calculated using Eq. (5):

$$\nu_t = Cf/2 \tag{5}$$

where C (mol dm^{-3}) is the concentration of cross-linking agent and f is the functionality of cross-linker. The value of C was determined from the concentration of cross-linker and density ρ of the xerogel. Direct weighing and micrometrically measured dimensions of the dried discs determined the latter. The Flory [3] swelling mode has been used in the literature to predict the molar mass between cross-links (Mc). This needs accurate values of Flory-Huggins interaction parameter χ. The temperature coefficient of volume fraction ($d\Phi_p/dT$) may obtained as in Eq. (6):

$$\begin{aligned}\left(d\Phi_p/d\,T\right) = {} & \chi\Phi_p\ T \\ & - 1\left\{2\Phi_p\chi - \Phi_p\left(1-\Phi_p\right) - \left[1\,n\left(1-\Phi_p\right) + \Phi_p + \chi\Phi_p 2\right]N\right\}^{-1}\end{aligned} \tag{6}$$

where,

$$N = \left(1/3\ \Phi_p\ 2/3 - 2/3\right)\left(\Phi_p\ 1/3 - 2/3\ \Phi_p\right)^{-1} \tag{7}$$

Solving Eqs. (6) and (7), we get the value of χ as follow (Eq. 8):

$$\begin{aligned}\chi = {} & \left[\Phi_p\left(1-\Phi_p\right)^{-1} + N\ln\left(1-\Phi_p\right) + N\ \Phi_p\right] \\ & \times \left[2\ \Phi_p - {\Phi_p}^2 N - {\Phi_p}^2\ T^{-1}\left(d\ \Phi_p/dT\right)^{-1}\right]^{-1}\end{aligned} \tag{8}$$

The molar mass between cross-links can then be estimated as in Eq. (9):

$$M_c = -\rho_p\ \nu_s\ \Phi_p\ 1/3\left[\ln\left(1-\Phi_p\right) + \Phi_p + \chi\ {\Phi_p}^2\right]^{-1} \tag{9}$$

where ν_s is the molar volume of solvent and ρ_p is the density of polymer. The υ_e calculated from Eq. (10):

$$\ln\left(1-\Phi_p\right)+\Phi_p+\chi\,\Phi_p{}^2+\nu_e\,\nu_s\left(\Phi_p{}^{1/3}-2\,\Phi_p\,f^{-1}\right)=0 \tag{10}$$

where ν_s (mol dm^3) is the molar volume of toluene at different temperatures T and obtained:

$$\nu_s=10^{-3}\left[\text{MWt of toluene}+3.6\times 1\,0^{-3}\,(T-298)\right] \tag{11}$$

Determination of χ thus allowed the effective cross-linking density (ν_e) to evaluate, thereby yielding the molar mass between cross-links (M_c) via Eq. (12):

$$M_c=\rho_p/\nu_e \tag{12}$$

Compression modulus of the prepared gels calculated according to Eq. (13).

$$G_T=RT\,\nu_e\,\Phi_p{}^{1/3}(V_u/V_f)^{2/3} \tag{13}$$

where R and T are the gas constant and absolute temperature and, respectively, V_u and V_f are volumes of dry unstrained xerogel and network at its formation, respectively. The correction factor $V_u/V_f=1$ as no solvent was included within the cross-linking reaction.

4 Applications of Cellulose-Based Hydrogel as Smart Corrosion Inhibitors

4.1 Introduction

The corrosion problem of metallic structures has become increasingly serious and extended to different fields [56–60]. As a common corrosion protection strategy, corrosion inhibitor generally is utilized because of its comfort, efficiency, and minimal cost. Corrosion inhibitors can adsorb on metal surface or react with corrosion products such as metallic ions to form insoluble complexes that significantly hinder further corrosion reactions. However, there are limits to development and application of the corrosion inhibitors. Corrosion inhibitor may hydrolyze weather and decompose during working process. Thus, this method would lead to the amount of inhibitor being too high toward the beginning and too low in the end. This not only wastes resources but also cuts down the productivity and maintenance time. In this manner, it is genuinely important to build up another inhibitor whose discharge procedure might activate when the corrosion happens and keeps up the quantity in a middling range in the long range. In the outline of an intelligent controlled-discharge inhibitor gadget, it is vital to make a smart on-off switch that can control the arrival of the inhibitor relying upon the outer boosts. Nowadays, hydrogel has been recognized as an interesting vehicle for delivery. Hydrogels encapsulating certain materials display an abrupt or piecemeal change in their

dynamic adjusting swelling properties as outside surrounding conditions change (such as pH, temperature), which are alluded to as smart materials [61–65]. Recently, pH-sensitive hydrogels are attracting more and more attention because they can exhibit phase transition in response to the changes of external pH. This property prompts pH-sensitive hydrogels to load drugs and control their release by external pH.

4.2 Evaluation Techniques for the Corrosion Inhibitors

The common for evaluation of the corrosion inhibitors are weight loss, hydrogen evolution reaction, open circuit potential, potentiodynamic polarization, and electrochemical impedance spectroscopy [66].

4.2.1 Weight Loss Technique

Triplicate specimens are cleaned and weighed before and after immersing in test solution with and without the investigated corrosion inhibitor at room temperature or at different temperatures. The specimens are removed, after specific times, then rinsed with water and acetone and dried. The loss of weight of the steel samples was determined using an analytical balance with the precision of 0.0001 ± 0.1 mg. The weight loss measurements are performed according to ASTM standard G 31–72. The percentage inhibition efficiency (IE) obtained from the following equation:

$$IE = \frac{W_\circ - W}{W_\circ} \times 100 \tag{14}$$

where $W_\circ$ and W are the weight of the specimen in the absence and in the presence of inhibitor.

4.2.2 Open Circuit Potential (OCP)

The open circuit potential (OCP), also referred to as the free corrosion potential, is the electrical potential difference between two conductors in a specific electrolyte with zero current flow between them. Monitoring the OCP over time can provide information about when the system has reached a steady state and when transitions between different states, such as passive and active behavior occur. In addition, OCP can provide information about the type of inhibitor whether the anodic or cathodic. According to Riggs [67], the classification of a compound as an anodic cathodic or mixed-type inhibitor is feasible when the OCP displacement is at least 0.085 V in relation to that one measured for the blank corrosive solution.

Figure 5 shows the variances of OCP of the carbon steel as a function of time in aerated 1 M HCl solution in the absence and presence of various concentrations of investigated inhibitor. The equilibrium potential is attained, corresponding to the free corrosion potential, E_{corr}, of the carbon steel. In inhibited 1 M HCl solution, the physical adsorption occurs between the positive charge of protonated inhibitor and negative charge of steel surface ($FeCl^-$). So the steady state E_{corr} drifts to more

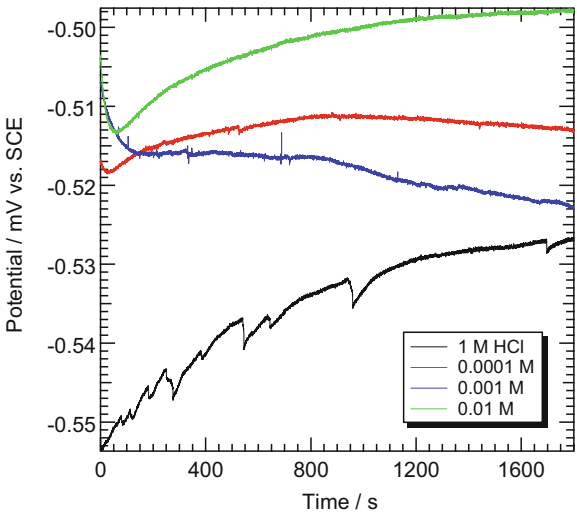

Fig. 5 OCP variation of steel versus time of in 1 M HCl and in the presence different molar concentrations of used inhibitor

positive values compared to uninhibited solution. However, the positive shift in E_{corr} is less than 0.04 V in the presence of the investigated inhibitors. This positive shift in Ecorr is too small for a reasonable classification based on OCP results. These findings reveal that the investigated inhibitors act decreasing both the anodic dissolution of iron and the hydrogen evolution reaction, i.e., mixed-type inhibitor [68].

4.2.3 Electrochemical Impedance Spectroscopy (EIS)

In general, EIS is a transient technique where an excitation applied to the system and the response (as a function of frequency) observed. EIS is a nondestructive technique that characterizes bulk and interfacial properties of all sorts of materials (conductors, insulators, and semiconductors). Many electrical parameters of the system can be determined in a single EIS experiment with an additional advantage that the signal averaged over long periods to achieve higher accuracy. Figure 6 represents the Nyquist diagram for the carbon steel in 1 M HCl in the absence and presence of various concentrations of investigated inhibitor.

All the impedance spectra exhibit one single capacitive loop, which indicates that the corrosion of steel controlled by the charge transfer process and usually related to the charge transfer of the corrosion process and double-layer behavior. In addition, the shape is the same throughout all tested inhibitor concentrations compared with that of blank solution. Thus, there is almost no change in the corrosion mechanism, whether the inhibitor is added. The diameter of the capacitive loop in the presence of inhibitor is larger than that in the absence of inhibitor and increases with the inhibitor concentration. This suggests that the impedance of inhibited substrate increases with the inhibitor concentration. Noticeably, these capacitive loops are not perfect semicircles, which attributed to the frequency dispersion effect because of the roughness and in homogeneousness of the electrode surface. In the Bode plots Fig. 7, only one time constant of charge transfer and double-layer capacitance is observed. This

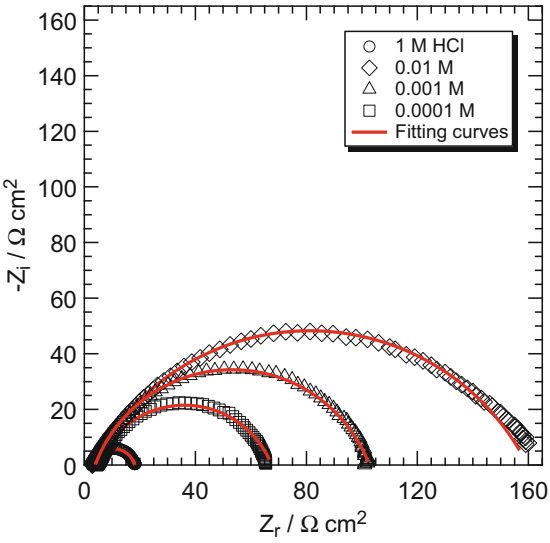

Fig. 6 Nyquist plots of carbon steel in 1 M HCl and in the presence different concentrations of inhibitor

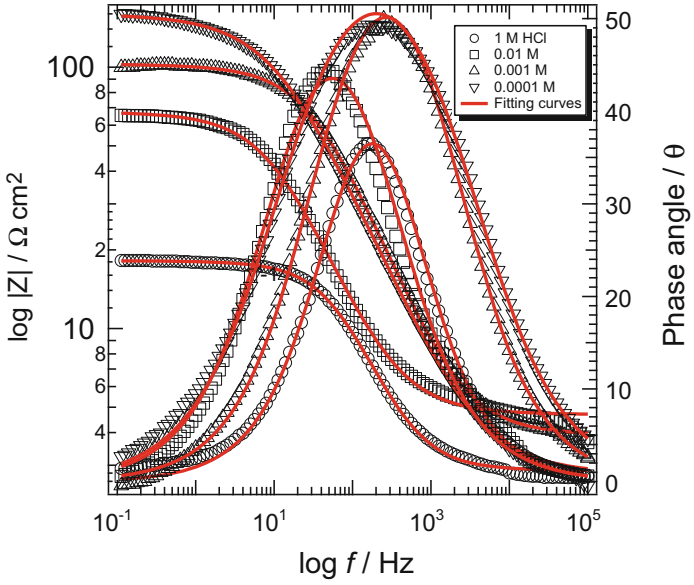

Fig. 7 Bode plots of carbon steel in 1 M HCl and in the presence different concentrations of inhibitor

observation indicates that the corrosion of the carbon steel in 1 M HCl solution is controlled by a charge transfer process. The slopes of |Z| against log *f* lines are not equal to −1. Again, this deviation attributed to the inhomogeneity of the carbon steel surface. Accordingly, the EIS data simulated the equivalent circuit shown in Fig. 8.

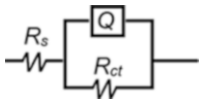

Fig. 8 Randles equivalent circuit applied for fitting of the impedance spectra

The R_s and R_{ct} are the solution resistance and charge transfer resistance, respectively. CPE is a constant phase element to replace a double-layer capacitance (C_{dl}) for more accurate fit. The CPE is composed of a component Q_{dl} and a coefficient n, which quantifies different physical phenomena like the surface in homogeneousness resulting from surface roughness, inhibitor adsorption, porous layer formation, etc. The double-layer capacitance (C_{dl}) is simulated via CPE from the following equation:

$$C_{dl} = Q_{dl} \times (2\pi f_{max})^{n-1} \tag{15}$$

where f_{max} represents the frequency at which the imaginary value reaches a maximum on the Nyquist plot. The R_{ct} increases prominently, while C_{dl} reduces with the concentration of inhibitor. A large charge transfer's resistance (R_{ct}) is associated with a slower corroding system. The inhibition efficiencies increase with the concentration of inhibitor.

4.2.4 Potentiodynamic Polarization (PP)

Potentiodynamic polarization is an electrochemical technique where the electrode potential is scanned continuously and the corresponding current density is recorded. The corrosion rate is evaluated through the Tafel extrapolation method. Potentiodynamic polarization curves of the carbon steel in 1 M HCl containing various concentrations are studied inhibitors shown in Fig. 9. The values of inhibition efficiency calculated according to the relation given below:

$$IE = \frac{i_o - i}{i_o} \times 100 \tag{16}$$

where i_o and i are uninhibited and inhibited corrosion current densities, respectively. Corrosion current densities are obtained by the extrapolation of the current-potential lines to the corresponding corrosion potentials. Herein, the corrosion rates are calculated assuming that the whole surface of the steel is attacked by corrosion and no local corrosion is observed.

By inspection of the polarization curves after the addition of inhibitor, it is observed that the current density of the anodic and cathodic branch displaced toward lower values and the displacement is more evident with the increase in concentration of the inhibitors. The addition of inhibitors to the corrosive solution (1 M HCl) both reduces anodic dissolution of iron and retards cathodic hydrogen evolution reactions as would be expected. This may be ascribed to adsorption of the inhibitor molecules over the steel surface. The parallel cathodic Tafel lines suggested that the addition of inhibitors to the 1 M HCl solution do not modify the hydrogen evolution mechanism

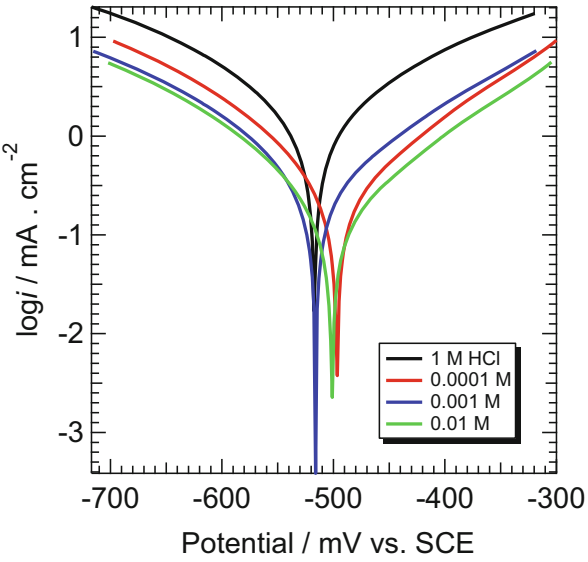

Fig. 9 Tafel plots of carbon steel in 1 M HCl and in the presence different concentrations of studied inhibitor

and the reduction of H^+ ions at the steel surface, which occurs mainly through a charge transfer mechanism.

4.3 Hydrogel as Control Release for Corrosion Inhibitor

Panpan Ren et al. [69] studied an intelligent corrosion inhibitor that was developed based on photo-cross-linked pH-sensitive poly(2-dimethylaminoethyl methacrylate) hydrogels (Fig. 10), which showed higher swelling at more acidic environment (pH = 2) and accordingly the corrosion inhibitor (benzotriazole) released a higher level (88%) for corrosion protection. The obtained intelligent corrosion inhibitor also demonstrated benefits in long-term corrosion inhibition because of more sustained benzotriazole supply. After 6 h immersion in 0.1 M Na_2SO_4 solution at pH = 2, a superior inhibitive effect to copper corrosion is found using the intelligent inhibitor than benzotriazole alone by showing a higher corrosion potential E_{corr} (25.34 mV vs. 10.19 mV), lower corrosion current density i_{corr} (0.20 μA/cm^2 vs. 0.68 μA/cm^2), higher critical breakdown E_b (144.34 mV vs. 107.19 mV) and higher polarization resistances Rp (77387.06 Ω vs. 34881.34 Ω) from polarization curves and larger capacitive are from Nyquist plots (Fig. 11).

Li et al. [70] also synthesized smart hydrogel pH-controlled-release corrosion inhibitor 1 H-benzotriazole (BTA). Figure 12 shows the details of the synthesis process. The scheme of synthesis process showed cross-linking reaction between acrylic acid (AA) and 2-hydroxy ethyl methacrylate (HEMA), and starch radical took place to attained three-dimensional networks of pH-sensitive hydrogel.

Equilibrium swelling of hydrogel was studied in solutions with various pH (Fig. 13a). It is found that this pH-sensitive hydrogel has high swelling capability

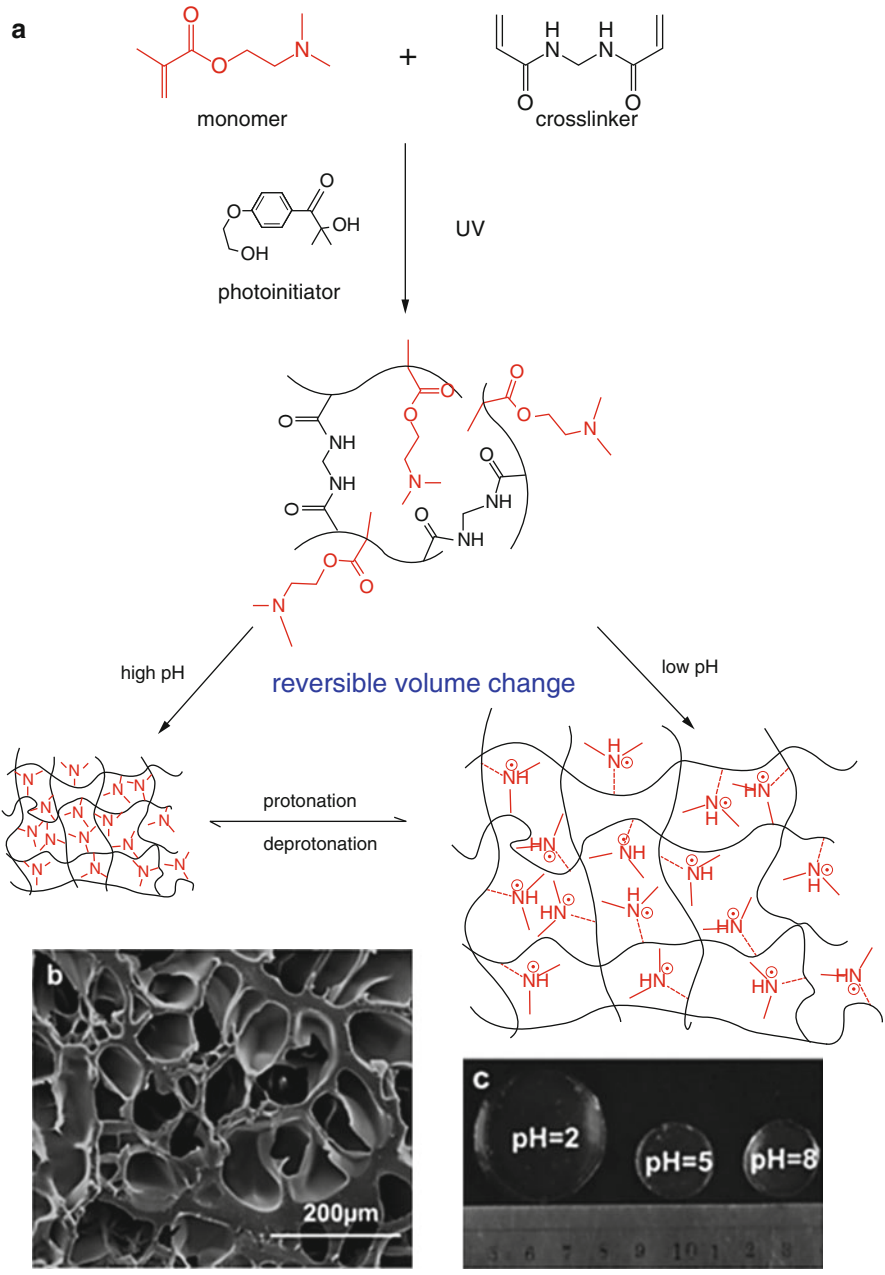

Fig. 10 (**a**) Molecular structure and reversible volume change of pH-sensitive poly (2-dimethylaminoethyl methacrylate) hydrogels; (**b**) SEM image of hydrogel disc; (**c**) hydrogel discs swollen at different pH

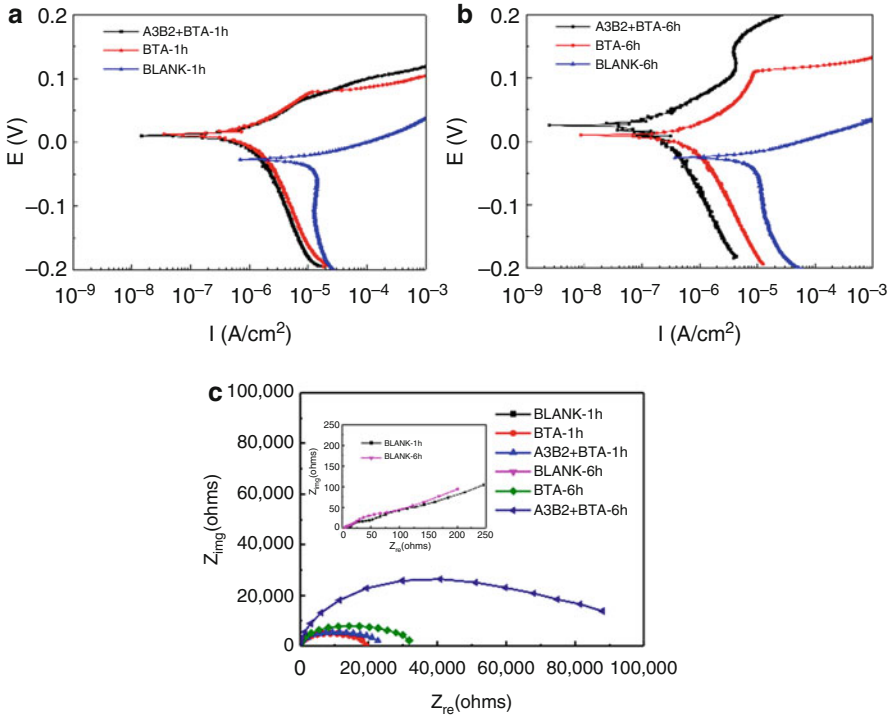

Fig. 11 Polarization curves and Nyquist plots of copper in 0.1 M Na_2SO_4 solution at pH = 2. (**a**) Polarization curves of 1 h; (**b**) Polarization curves of 6 h; (**c**) Nyquist plots of 1 h and 6 h

in basic solutions but low in acidic ones. This is mainly because of the force between the same charge ions. In acidic medium, most of carboxylate groups are protonated, so the decreased repulsion of anionic groups leads to a decreased swelling rate. When medium pH increases, carboxyl groups of acrylic acid convert to COONa groups and then ionize depending on the medium pH. The reason for swelling-loss in highly basic solutions is the "charge screening effect" of excess Na^+ in swelling media, which shields carboxylate anions and prevents effective anion-anion repulsion. As shown in Fig. 13b, a fast and reversible swelling-deswelling behavior is observed due to the deprotonation and protonation of carboxylate groups at pH 8.0 and pH 1.0, respectively. This controllable swelling ability of the hydrogel makes it appropriate for controlled-release system.

The drug release of the hydrogel entrenching 1H-benzotriazole (BTA) as corrosion inhibitor is measured through immersing drug-loading hydrogel in different pH solutions, as shown in Fig. 14a. Cumulative release of BTA from hydrogels was relatively low in pH 1.0 solution (29% for 24 h). While in pH 8.0 solution, the release of BTA went up considerably with the swelling of hydrogels (80% for 24 h). The release of BTA for pH 6.0 and pH 7.0 was in the range 55–65%, respectively, for 24 h. The working mechanism is presented in Fig. 14b. When the environment was

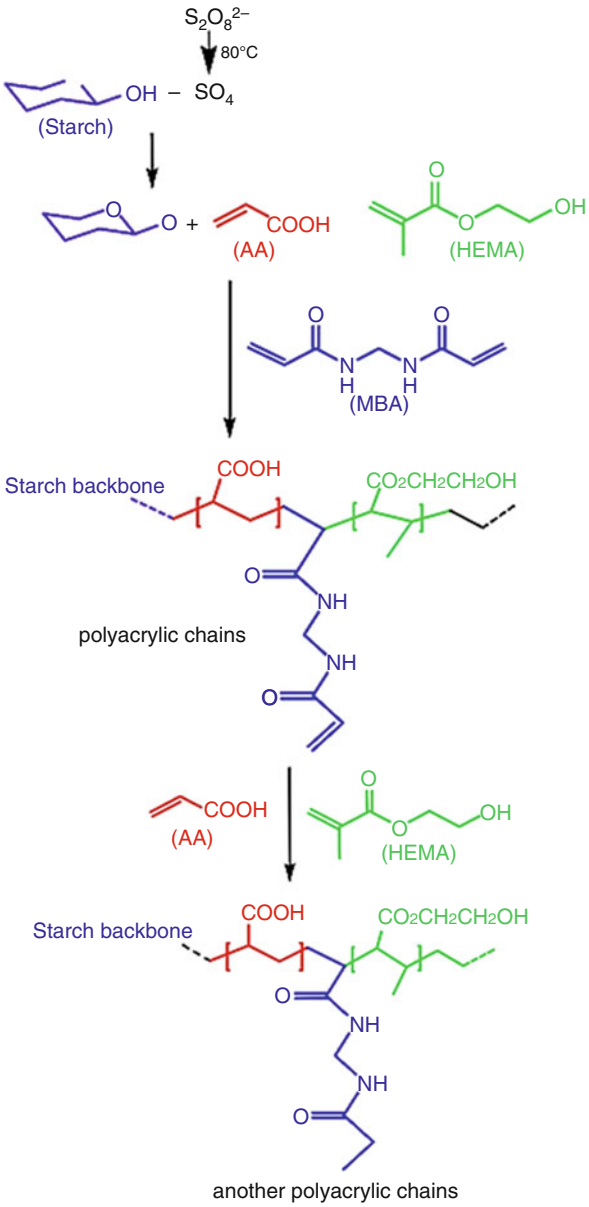

Fig. 12 Details of 3-D networks reaction

alkaline, the hydrogel swelled and corrosion inhibitor embedded in the hydrogel would release. While in acidic media, the hydrogel is de-swelled and corrosion inhibitor is preserved.

The protection of BTA and intelligent inhibitor was detected using polarization curves. Typically, lower E_{corr} and higher I_{corr} indicate a more serious corrosion.

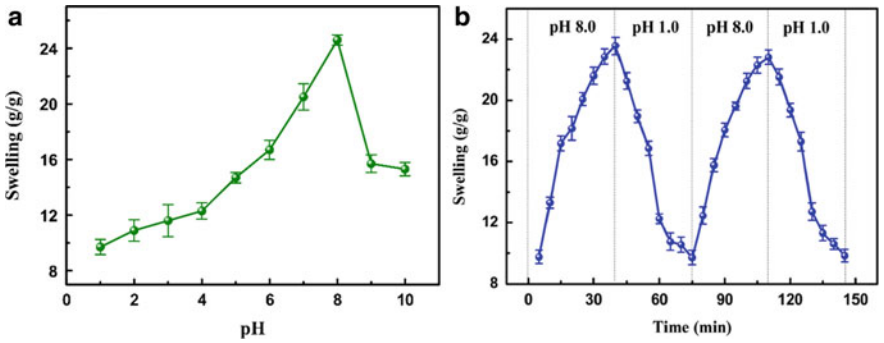

Fig. 13 (**a**) Effect of solution's pH on swelling of starch-g-poly(AA-co -HEMA) hydrogel and (**b**) the swelling-deswelling reversibility of the hydrogels

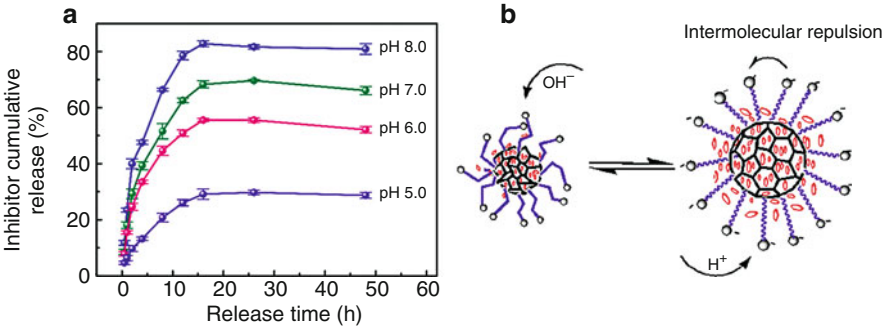

Fig. 14 (**a**) The release curve of the BTA corrosion inhibitor and (**b**) the working mechanism of the pH-controlled-release intelligent corrosion inhibitor

Figure 15a shows the polarization curves of aluminum immersed in 3.5% NaCl (pH 8.0) for 1 h with BTA and intelligent inhibitor, and Fig. 15b presents the polarization curves of aluminum immersed in 3.5% NaCl (pH 8.0) for 5 h. In the first 1 h, it obviously showed that the E_{corr} with BTA inhibitor was higher than that of intelligent inhibitor. This indicated that BTA inhibitor played an important role in the protection, while the intelligent inhibitor did not show favorable performance because hydrogel was swelling and the embedded BTA could not release quickly. BTA inhibitor still displayed a protection to a certain extent after 5 h; however, intelligent inhibitor performs more perfect protection to the electrode.

The surface morphology of aluminum before and after immersion in 3.5% NaCl solution (pH 8.0) with different inhibitors is presented in Fig. 15c–e. According to the images, there are much more pits on the sample surface with BTA inhibitor than that with intelligent inhibitor. Moreover the pits formed seen on Fig. 15e are deeper and bigger than on Fig. 15d. Therefore, the intelligent inhibitor has a more outstanding corrosion resistance in a relatively longer time.

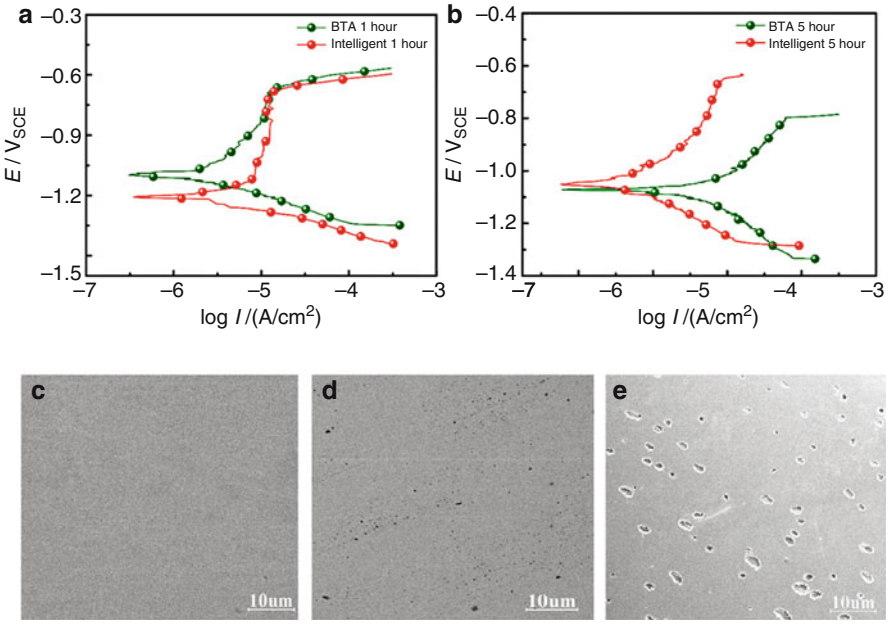

Fig. 15 The polarization curve of 7A04 aluminum alloy with different corrosion inhibitor for (**a**) 1 h and (**b**) 5 h. The surface morphology of 7A04 aluminum alloy immersed in 3.5% NaCl solution (**c**) before (**d**) with intelligent inhibitor for 5 h (**e**) with BTA inhibitor for 5 h

T. Gu et al. [71] prepared excellent performance of polyvinyl alcohol hydrogel in terms of controlled-release and corrosion-scale inhibition. Particle PVA with a ratio of about 1 g to 3 mL distilled water will make the preparation of PVA hydrogel more convenient and faster during the commercial process.

The results of releasing experiments at various temperatures confirm the general trend in solubility dependencies for common hydrogels. The increase in PVA solubility can be caused by a temperature rise of 10–70 °C which is in an allowable range as the field temperature is only about 40–60 °C; therefore, the PVA hydrogels will be a sustainable release carrier in the pipeline system of oil field (Fig. 16).

Scale inhibition efficiencies of the PVA matrix inhibitor releasing in two different systems (PE bottles and the simulated pipeline system) are shown in Fig. 17. As it is seen, both systems had sustainable anti-scale rate, indicating the stable release, which confirmed the utility of PVA-based inhibitor in oil fields. The corrosion inhibition performances of PVA hydrogel were tested (Fig. 18). Once the hydrogel put into water, imidazoline escaped quickly from the surface of PVA hydrogel into water, which led to a higher concentration of imidazoline in corrosion solution and thus better performance of anticorrosion.

Jie Hu et al. [72] prepared pH-sensitive core-shell organic corrosion inhibitor (COCI) based on poly(ethylene oxide)-b-polystyrene (PEOb-PS) copolymers and studied its release behavior in simulated concrete pore solutions. PEO-b-PS diblock

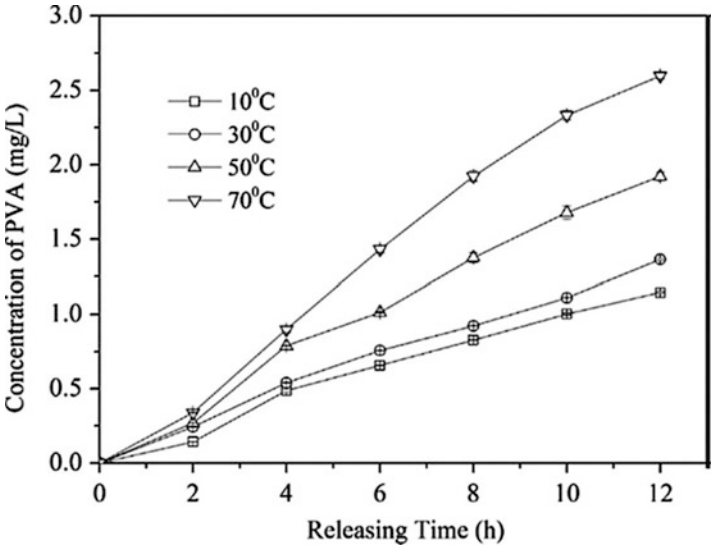

Fig. 16 The releasing performance of PVA hydrogel at different temperatures

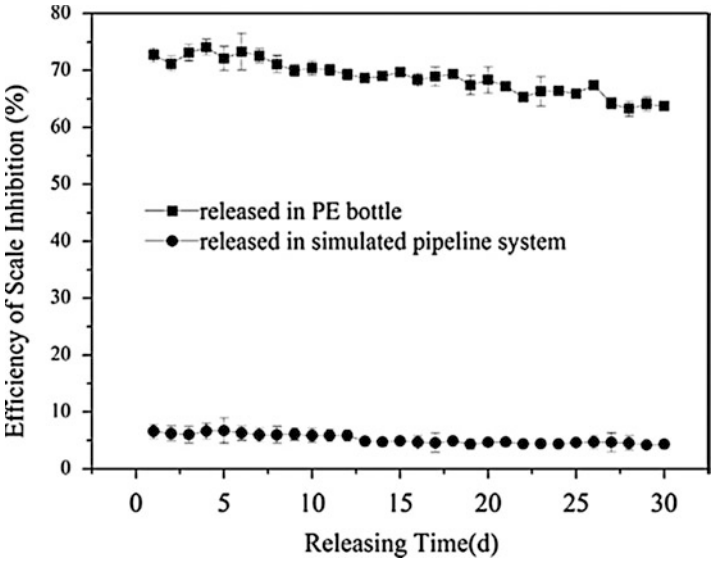

Fig. 17 Scale inhibition efficiency of solid inhibitor releasing in two different ways

copolymers used in this study synthesized by atom transfer radical polymerization (ATRP), as shown in Fig. 19.

Esterification reaction between PEO-OH and 2-bromoisobutyryl bromide produces macroinitiator PEO-Br. Then PEO-Br initiated the polymerization of styrene

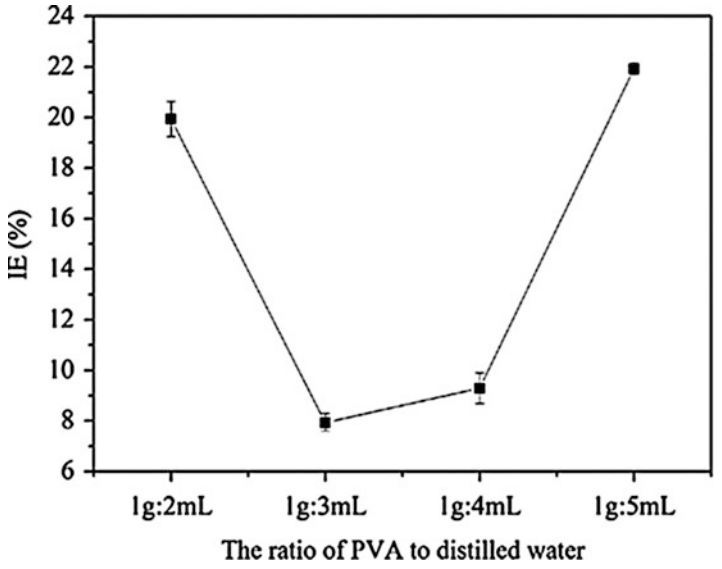

Fig. 18 The corrosion inhibition efficiency for different ratios of PVA to distilled water

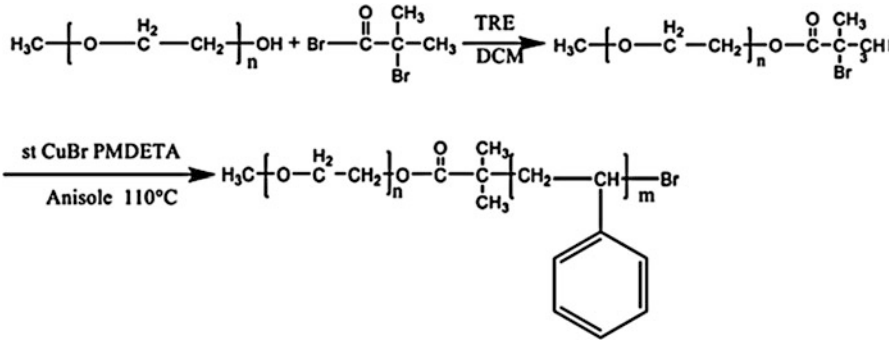

Fig. 19 Synthetic route of PEO-b-PS copolymers

to form PEO-b-PS diblock copolymers. The prepared PEO-b-PS diblock copolymers have amphiphilic formations, presenting hydrophilic PEO chain and hydrophobic PS chain. Therefore, PEO-b-PS copolymers have self-assembly property and can form vesicles with PEO shell and PS core at the interface between organic solvent and water. As shown in Fig. 20, during the self-assemble process, benzotriazole (BTA) as the organic corrosion inhibitor is encapsulated in the vesicles to prepare the core-shell corrosion inhibitors.

The release amount of BTA reserved in COCI in deionized water with different pH values is shown in Fig. 21.

It is observed that the release rate of BTA is influenced by the pH value of deionized water: in deionized water with higher pH values (11 and 13). The

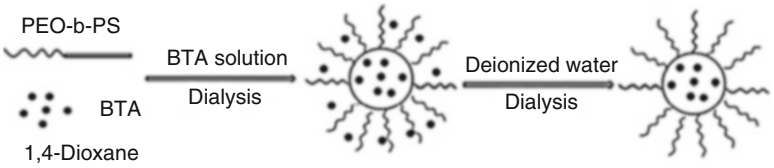

Fig. 20 Preparation route of COCI

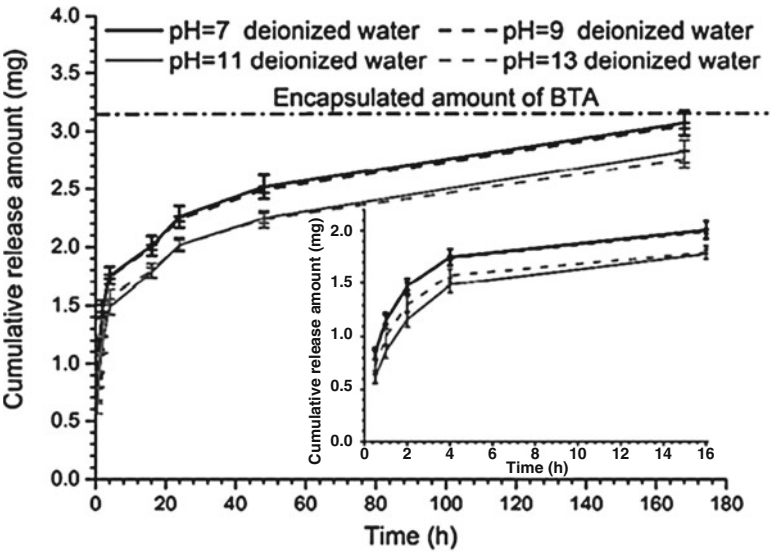

Fig. 21 Release profiles of BTA in deionized water with different pH values

accumulative release amount of BTA was about 2.80 mg up to 7 days; in deionized water with lower pH values (pH = 7 and 9). The release rate of BTA accelerated, and the accumulative release amount was about 3.05 mg after 7 days, which was about 96.86% of the encapsulated BTA amount (3.15 mg in 3 ml COCI solution, the dash line in Fig. 21) in COCI. The accumulative release amount in deionized water with lower pH values (pH = 7 and 9) was about 9% higher compared to that with pH values of 11 and 13 up to 7 days.

The release amount of BTA in simulated concrete pore (SCP) solutions with different pH values is resented as shown in Fig. 22. In SCP solution with a pH value of 13, the accumulative release amount of BTA was only about 0.5 mg up to 3 days. However, in SCP solutions with lower pH values (pH = 7, 9, and 11), the accumulative release amount of BTA is in the range of 2.5–2.8 mg, which means most of the encapsulated BTA (3.15 mg) was released, and the release amount was five times higher than the release amount of BTA in SCP solution with a pH value of 13.

In order to confirm the more pronounced pH sensitivity of COCI, after immersed in SCP solution with a pH value of 13 for 3 days, the dialysis bag was then immersed

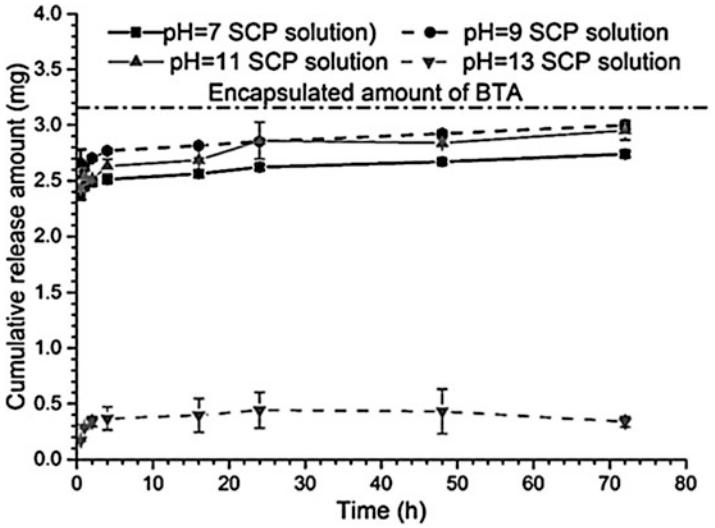

Fig. 22 Release profiles of BTA in SCP solution with different pH values

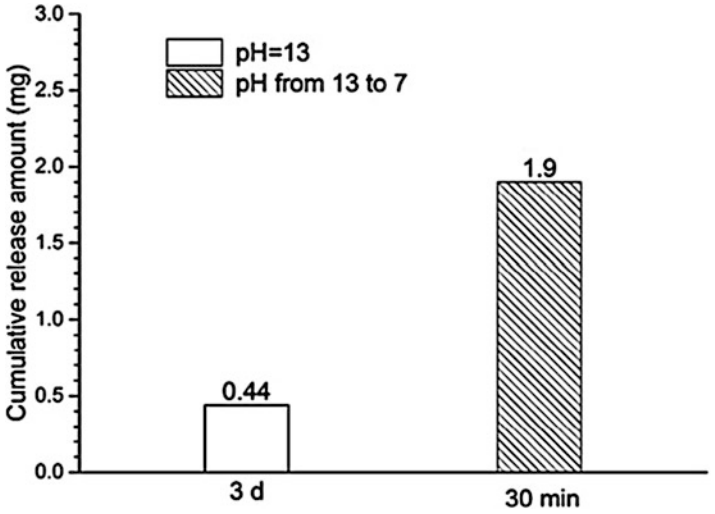

Fig. 23 Release amount of BTA in SCP solution with a pH value of 7 after immersed in SCP solution with a pH value of 13 for 3 days

in SCP solution with a pH value of 7 for further investigation, and the result is shown in Fig. 23.

Immediately after the dialysis bag was immersed in SCP solution with a pH value of 7, BTA reserved in COCI was rapidly released: only after 30 min, a huge amount (1.9 mg) of BTA was released into SCP solution. This is consistent with the data

shown in Fig. 22. The results indicate that the release process of BTA was very sensitive to the pH alteration in simulated concrete pore solution: when the pH value of SCP solution was 13, BTA stably encapsulated in COCI; when the pH value of SCP solution dropped to below 11, the release rate of BTA was dramatically accelerated.

Finally, the release rate of BTA was significantly accelerated in simulated concrete pore solution, and a large proportion of BTA reserved in COCI was released (Fig. 17). The released BTA can possibly halt corrosion propagation, leading to an increased corrosion resistance of the steel reinforcement. Therefore, the prepared core-shell organic corrosion inhibitors in this study are potentially used for the spontaneous corrosion protection in reinforced concrete (due to its controlled-release behavior in SCP solutions).

Cellulose is crystalline in nature. In desirable quantities, it is used as a modifier rendering toughness in fragile coatings. The primary hydroxyl groups present in the chain may further facilitate adhesion to the substrate hydrophobicity-modified hydroxyethyl cellulose used in WB coatings and paints provided good gloss [73]. Films are obtained from regenerated cellulose (from cotton linter) by coating. Ethyl cellulose-based aqueous dispersions and solvent-based films were plasticized with *n*-alkenyl succinic anhydrides -2-octenyl succinic anhydride (OSA) and 2-dodecen-1-ylsuccinic anhydride to overcome the brittleness of cellulose films [74]. Films obtained showed excellent mechanical properties, low permeability, and good flexibility. Amoxicillin-doped cellulose acetate films showed good corrosion resistance on AA2024-T3 substrate [75]. Films doped with 2000 ppm of the drug showed good anticorrosion behavior as observed by electrochemical impedance spectroscopy [EIS] results. These films showed lower current densities up to 3 days of immersion under anodic polarization. Scanning vibrating electrode technique [SVET] results are found to be in close agreement with EIS and polarization results, also informing about the defects in coating. The results also showed a decrease of the electrochemical activity in the doped cellulose acetate films, relative to their undoped counterparts. Liu et al. prepared cellulose acetate phthalate-free films with diethyl phthalate/triethyl citrate as the plasticizer by spray method under heat only (50 °C for 24 h) and heat-humidity curing (50 °C/75% RH for 24 h) conditions [76]. The latter (despite retaining higher content of plasticizer due to suppressed evaporation) provided increased mechanical strength and decreased water vapor permeability of the films. Triethyl acetate films showed increased % elongation, decreased tensile strength, and elastic modulus relative to diethyl phthalate films; however, the latter showed low permeability.

Forming a persistent passive film on the surface of the steel bars is one of the most desirable properties in terms of corrosion protection in reinforced concrete. If a microcapsule possesses such a property, it is employable in prolonging concrete's durability, especially in corrosion protection of the embedded steel bar. In order to confirm its feasibility, the experimental results are shown as follow.

To summarize, the microcapsule-based self-immunity system has been found to be a promising prospect for corrosion protection applications, which is ensured by smart interaction between the system's $[Cl^-]/[OH^-]$ value and corrosion initiation.

For microcapsule fabrication, one should note the materials of the core and shell, which are the main functional representation. Another point is the basic properties of microcapsules, namely, size and appearance. These factors also contribute to the functionalization of the microcapsules.

The release process and release characteristics of the microcapsules are strongly responsible for corrosion protection. The release investigation indicates that such a self-immunity microcapsule can be triggered by low pH values, and calcium hydroxide can controllably release to regulate the environmental pH condition. Additionally, ESEM observation analysis conducted at different times and pH values. Test results show that the microcapsule release process is a function of time. Moreover, the release rate of core materials could interact with environmental pH value; the rate increases markedly with decreasing pH value but inhibited by high pH values.

Conventionally, the direct addition of corrosion inhibitors to the reinforced concrete is to bind or combine chloride for reducing the $[Cl^-]/[OH^-]$ ratio. However, some drawbacks will appear due to the direct application of corrosion inhibitors. The solubility of a corrosion inhibitor plays a very important role in determining the efficiency of the protection it can provide. Low solubility may result in a poor rust protection effect because of the lack of the active agent, whereas high solubility of corrosion inhibitors will cause premature reactions during hydration of the cement, which could adversely influence the composition and microstructure of the hydration products. Meanwhile, consumption of a certain amount of corrosion inhibitor at an early age leads to less availability of the agent to bind the chloride at later stage. In this kind of microcapsule, a core agent containing hydroxyl ions is encapsulated in order to prevent premature reactions with other components during the early-age hydration of the cement. More importantly, a pH-sensitive shell material is selected to control the release of the hydroxyl ions. The ethyl cellulose (EC)/calcium hydroxide microcapsule satisfies these requirements and is thus suitable for regulating the hydroxide concentration in cementations materials [77].

Cellulosic polymers as green materials show significantly assured anticorrosion manners [78]. Widespread studies for anticorrosive film-based cellulose are shown [79–82]. Shih and Chieh [83] evaluate the anticorrosion performance of biopolymer hydroxypropyl methylcellulose (HPMC) derivatives in a saline solution. Meanwhile, HPMC has a good capability for distributing and preventing grease and gas penetration [84] and is used in sustainable manufacturing [85]. Moreover, owing to its biocompatibility [86] and decomposability [87, 88], it is also used as a corrosion inhibitor [89–92]. Traditional HPMC is soluble in water; thus, it is not suitable for a water and high humidity environment. It usually added to liquid as a corrosion inhibitor. In the sustainable manufacturing applications, solid films are used to replace the solution-type inhibitor for the environmental-friendly considerations. Therefore, acetate, succinate, and phthalates are added to HPMC to obtain hydroxypropyl methylcellulose phthalate (HPMCP) and hydroxypropyl methylcellulose acetate succinate (HPMCAS). They not only preserve the characteristics of HPMC but also are also insoluble in water and function well in strong acid environments.

5 Conclusions

Firstly, this chapter gives general information about the hydrogel definition, classifications, cross-linked structure of hydrogel, and types of polymers used for forming hydrogel. In addition, it described a brief overview of hydrogel-based on cellulose, definitions, methods of preparation, and applications as smart corrosion inhibitors as discussed in some detailed in the text. Therefore, the core-shell organic corrosion inhibitor-based cellulose in this study can be used for the spontaneous corrosion protection in reinforced concrete due to its controlled-release behavior in SCP solutions.

The corrosion resistance performances of green polymer material HPMC derivatives are demonstrated. A pH-sensitive shell material is selected to control the release of the hydroxyl ions. The ethyl cellulose (EC)/calcium hydroxide microcapsule satisfies these requirements and is thus suitable for regulating the hydroxide concentration in cementations materials. Traditional cellulose-based polymers are soluble in water; thus, it is not suitable for a water and high humidity environment. It is usually added to liquid as a corrosion inhibitor. In the maintainable industrial applications, solid films (hydrogel-based on cellulose) are used to exchange the solution-kind inhibitor for the environmental-friendly considerations.

6 Future Scope

Smart materials based on cellulose show intelligent behaviors in response to enabling them to apply in many fields. Stimuli-responsive materials based on cellulose still needs to become the focus of more studies because the excellent properties allow the materials to be applied in many fields, especially in bio applications. Though excellent structure of smart polymers based on cellulose has been applied in various fields, more work still needs to be done to make them more practical.

For future studies, more attention should focus on the following:

- Dissolution of cellulose based on green solvents, nontoxic cross-linkers, and/or low-energy processing for hydrogel systems.
- Injectable hydrogels forming safely within the body without the need of surgery for targeting drug release or tissue engineering.
- pH or enzymatic triggered drug release at targeted sites.
- Hydrogel degradation in a controlled manner in tissue engineering or sustained drug release.
- Hydrogels based on cellulose still offer abundant talented chances in several industries; thus, essential investigation based on the nature of these ecofriendly polymers should also continue.
- Development of new applications of green hydrogel systems, e.g., polyelectrolyte complex hydrogels as electrical elements.

- Development of hydrogel functionalization as an economical way to improve efficacy, selectivity, or recycling during water purification.
- Synthesis of smart hydrogels based on cellulose encapsulation for coatings and corrosion protection in oil field.

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Cellulose-Based Hydrogels for Water Treatment

32

Ilker Yati, Soner Kizil, and Hayal Bulbul Sonmez

Contents

Abstract

Lakes, rivers, sea, groundwater, drinking water basins, etc. are the main water sources which can increasingly be polluted by commercial and industrial establishments or human activities. The most existing types of contaminants that pollute these water sources are dye-containing effluents and toxic heavy metals which they affect living being's life catastrophically. Various methods have been applied to get rid of these kinds of toxic pollutants from water sources such as reverse osmosis, chemical precipitation, membrane filtration, coagulation, ion exchange, electrochemical treatment, and adsorption. Among these methods, adsorption is quite effective and economic method for the removal of toxic pollutants. Hydrogels that can be described as 3D network of hydrophilic polymer chains cross-linked chemically or physically which are able to soak and release a significant amount of water while preserving their network structure from dissolution in aqueous media, and they can be applied in many fields

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including tissue engineering, drug delivery, wound dressing, food, cosmetics, contact lenses, sensors, and water treatment. Hydrogels are excellent candidate to remove toxic pollutants by adsorption due to their high absorption capacity, porous structure, rich functional groups, and relatively low crystallinity. These hydrogels can be composed of petroleum-derived synthetic polymers, natural occurring materials, or composition of both synthetic and natural materials. Hydrogels that prepared from natural materials are preferred by their low cost and biodegradability and easily available from plenty of resources. To prepare hydrogels, a wide range of synthetic and natural materials have been used, such as cellulose, chitin, and chitosan for natural materials; polyethylene glycol and poly (sodium acrylate) for synthetic materials can be given as an example. Among them, cellulose is a well-known naturally found linear homopolymer having consecutive glucose units connected by glucosidic bond. The use of cellulose-based hydrogels is gaining popularity because of their several advantages such as environmental friendliness, biodegradability, biocompatibility, nontoxicity, easy availability, high abundance, low cost, and thermal and chemical stability for water treatment applications. Therefore, cellulose-based hydrogels have been attracted much attention in both academic and industrial applications including drug delivery, hygiene products, medicine, and water purification technologies. Among these applications, the use of cellulose-based hydrogels for water treatments has been discussed in this chapter.

Keywords
Cellulose · Hydrogel · Heavy metal · Dye · Water pollution · Adsorption

1 Introduction

Modern civilization has caused the fast deterioration of our environment due to its rapid increase in the population and industrialization. Water is the most essential and one of the precious natural sources we need on this planet. The pollution of water can be occurred when its quality or compositions are affected by waste disposal, industrial effluents, or human activities. Therefore, its odor, color, taste, or content might be changed, and it becomes hazardous for drinking, domestic, and agricultural usage. Water pollutants which originate from industrial effluents, human activity, sewage disposal, and so forth include almost all kinds of toxic substances ranging from simple organic matter to complex ones such as silt, toxic heavy metals, dyes, pesticides, oils, etc. [1, 2]. Those contaminants are dangerous for marine species, plants, as well as humans and can cause serious health problems such as cancer, organ damage, nervous system damage, diseases of kidneys, and circulatory system and brain damage [3]. The resulting hazardous effects by this kind of polluted waters need to be addressed, and those polluted waters must effectively be cleaned up using appropriate methods.

Gels are cross-linked polymeric network that store large amount of liquids. They are wet and soft and look like a solid material but are capable of undergoing large

deformations [4]. When the liquid is an organic solvent, the gel is defined as an organogel [5–8]. However, the liquid is water, and then it can be defined as hydrogel. Owing to sophisticated features of hydrogels including high water content and the porous network structure, they can be widely used in various applications such as personal care products, agriculture, sensors, drug delivery systems, and sorbents for environmental applications [9, 10]. Hydrogels can be classified as synthetic, semi-synthetic, and natural, depending on the source of initial material. A variety of synthetic and natural materials, including polyethylene glycol (PEG), polyacrylamide, poly lactic acid (PLA), and polyvinyl alcohol (PVA) as synthetic and chitosan, hyaluronic acid, cellulose, etc. as natural, have been extensively employed to synthesize hydrogels [11–13].

Among the natural materials, cellulose which can be produced from plants including cotton, banana, orange peels, and rice husk and from bacteria including *Acetobacter*, *Rhizobium*, *Agrobacterium*, *Sarcina*, *Pseudomonas*, *Achromobacter*, *Alcaligenes*, *Aerobacter*, and *Azotobacter* [14], most abundant natural polymer on earth, is a natural polysaccharide composed of β-1,4-glucosidic bonds in the polymer chain and is environmentally friendly, biocompatible, green, inexpensive, and sustainable material. Thus, these materials have great potential for applications in wide fields because they can be chemically functionalized with respect to the intended use.

In recent years, polymeric gels, especially natural-derived polymers due to its low cost and high abundance, have been widely used in different applications including drug delivery systems, sensors, water treatments, medical technology, agriculture, and oil sorbents [15–17]. Polysaccharides and their derivatives are one of the most used natural materials because they can be easily obtained from plants or animals. For example, Ummartyotin et al. [18] have prepared cellulose-based hydrogel, and they have found that the obtained hydrogels presented excellent features including good thermal stability, chemical resistance, and mechanical properties. The swelling ratio of synthesized hydrogels was found to be 400–600%. Essawy et al. [19] produced a novel bio-based adsorbent by graft copolymerization of acrylic acid onto cellulose in the presence of fulvic acid as interpenetrating agent. The obtained adsorbent is used for the removal of Cu^{2+}. In another study, cellulose which was extracted from rice husk was chemically modified and used for CO_2 capture by Einloft et al. [20].

2 Toxic Pollutants in Water

With rapid population growth and industrialization, the environment is becoming more polluted, and this problem has significant negative effect on economy, human life quality, and environment.

Water pollution by organic contaminants has been one of the most concerning threats needing to be solved by mankind [6]. Oil and petroleum derivatives from oil leakage events, dyes from textile industries, and heavy metals from factory wastewater have become one of the most common pollutants in wastewater. These pollutants affect human life and environment negatively, and many of them are

known to be toxic or carcinogenic for human life. For example, mercury is known one of the most toxic heavy metals for environment. Also, heavy metals including mercury and cadmium are not biodegradable which cause various diseases and disorders on the human body [21]. Moreover, the presence of synthetic dyes may cause skin irritation which can cause severe damage to human beings including dysfunction of the kidneys, reproductive system, liver, brain, and central nervous system, and because of that, they are classified as toxic and carcinogenic [22, 23]. Polycyclic aromatic hydrocarbons (PAHs) are organic compounds that are composed of multiple aromatic rings and are persistent in the environment because of their chemically stable structure. Due to that, they are known as carcinogenic, mutagenic, and toxic materials [24].

The presence of organic contaminants in water is a serious problem. The organic contaminants such as dyes and oils on the water surface can severely impact on the environment of marine life (by inhibiting the penetration of sunlight) as well as on human life (by adversely impacting on fishing, coastal beaches, resorts, etc.) [6].

Bearing in mind that the mentioned chemicals have adverse effect on human life and environment, the removal of such pollutant from wastewater is urgently needed for living organisms and environments [25, 26].

3 Techniques for the Removal of Toxic Pollutants

Water pollution is defined as chemical, biological, and physical change in water resources which reduce the quality of living organisms and make the water unsuitable for human activity. Many of the matter can cause the pollution such as synthetic dyes, heavy metals, pesticides, polycyclic aromatic hydrocarbons, and so on. General classification of water pollutants has been summarized in Table 1. Wastewater with organic pollutants contains a sleeve of harmful materials which may inhibit the penetration of sunlight, change the characteristics of water, and adversely impact the human life on fishing, coastal beaches, and resorts.

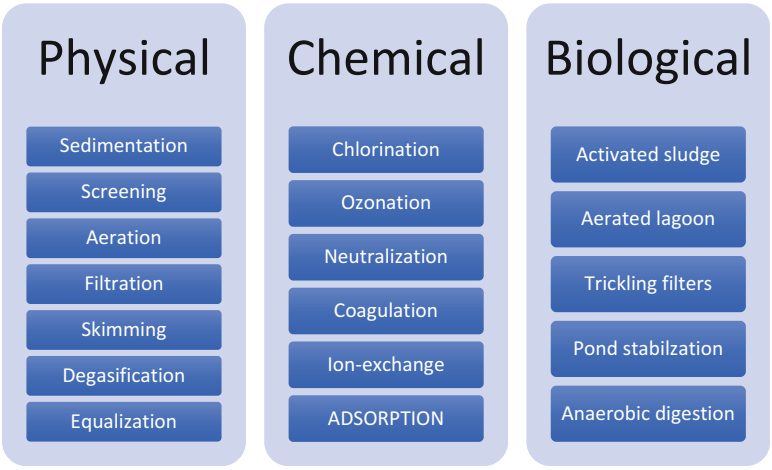
Wastewater treatment methods can be classified in three parts including physical, chemical, and biological process (Table 2). Currently, several effective chemical techniques to remove these kinds of pollutants have been used and fabricated by many researchers.

All these techniques have some advantages and disadvantages as listed in Table 3. Among the abovementioned techniques, adsorption is considered to be the most effective method because of multiple benefits such as easy to perform, convenient, no undesirable by-product formation, and high and quick sorption ability [28]. However, adsorption efficiency depends on the type of adsorbent. Although activated carbon-based materials have been recognized as one of the most used adsorbents for the removal of organic pollutions, some parameters such as reusability, cost, etc. restrict their use for the removal of such pollutants. Gels are cross-linked macromolecules that are an important class of soft materials; they can absorb a large amount of liquids within their three-dimensional network structure, so, they are becoming promising materials as adsorbents for the wastewater treatment [5].

Table 1 Classification of water pollutants [27]

Generation	Nature	Examples
Physical	Color	Dyes, pigments
	Suspended or floating matters	Sand, silt, wood chips, paper, etc.
Chemical	Organic	Plastic, tar, pesticides, oil, etc.
	Inorganic	Nitrates, phosphates, heavy metals, fluorides, etc.
Biological	Pathogenic	Bacteria, virus, worms, etc.

Table 2 Wastewater treatment methods



While water treatment costs of other technologies including reverse osmosis, ion exchange, and electrodialysis range from 10 to 450 US$ per cubic meter of treated water, adsorption methods need 5–200 US$ per cubic meter of water [29].

Different types of materials have been used to adsorb pollutants from wastewater. Recently, there are highly increasing interests in low-cost materials to use as sorbents for the removal of organic pollutants from wastewater [32]. For this reason, natural materials from plants and animals have been increasingly studied as adsorbents for the removal of organic and inorganic pollutants.

4 Cellulose-Based Hydrogels for Removal of Pollutants from Wastewater

A variety of materials have been investigated as sorbents for the cleaning of pollutants from wastewater. Several reports have indicated that cellulose-based hydrogels are considered to be ideal materials for the removal of different inorganic or organic pollutants such as heavy metals, organic solvents/oils, antibiotics, dyes,

Table 3 Advantages and disadvantages of water treatment techniques

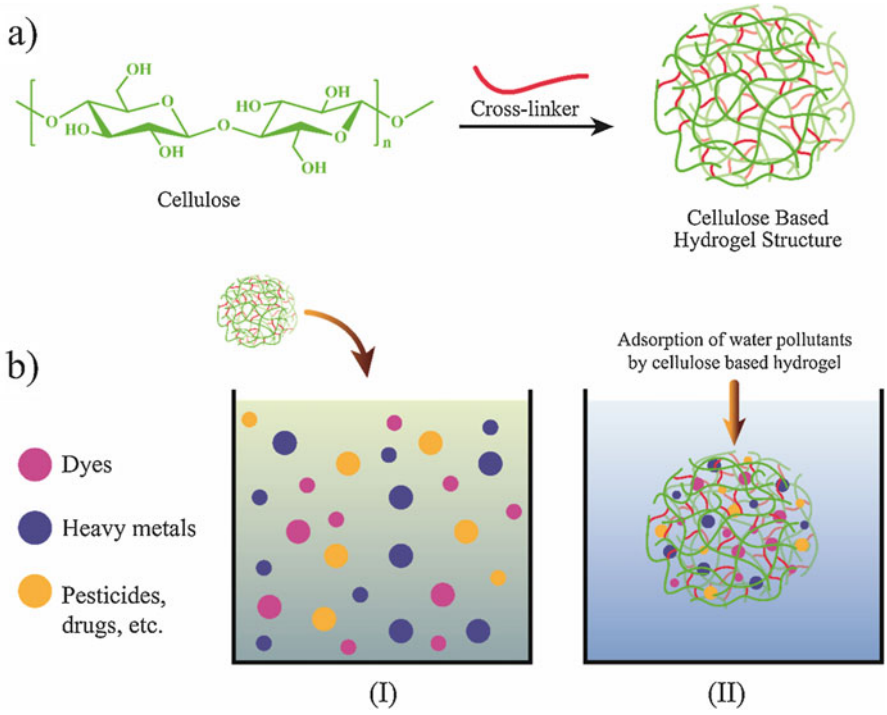
Physical and/or chemical methods	Advantages	Disadvantages [30, 31]
Oxidation	Rapid process for toxic pollutant removal, it does not require pre- and posttreatment	High energy costs and formation of by-products
Ion exchange	Good removal of a wide range of heavy metals and dyes, energy requirements are minimal	High operating and chemical costs, high sensitive to fouling
Membrane filtration technologies	Good removal of heavy metals and dyes	Concentrated sludge production, expensive, requires periodic cleaning
Coagulation/ flocculation	Economically feasible	High sludge production and formation of large particles
Electrochemical treatment	Rapid process and effective for certain metal ions	High energy costs and formation of by-products
Ozonation	Applied in gaseous state: alteration of volume	Short half-life
Photochemical	No sludge production	Formation of by-product
Irradiation	Effective at lab scale	Requires a lot of dissolved O_2
Electrokinetic coagulation	Economically feasible	High sludge production
Fenton's reagent	Effective and capable of treating a variety of wastes and no energy input necessary to activate hydrogen peroxide	Sludge generation
Biological treatment	Feasible in removing some metals	Technology yet to be established and commercialized
Adsorption	Universal, easy to operate, low cost, can achieve nearly 100% water recovery	Adsorbents require regeneration

and other pollutants [33–36]. Schematic representation of cellulose-based hydrogel network and the removal of pollutants by this hydrogel was given in Scheme 1.

It was known that hydrogels should have some parameters to use as adsorbents in wastewater applications including high swelling capacity, high adsorption capacity, and high physical, chemical, and mechanical stability and reusability [37].

4.1 Removal of Heavy Metals

Water sources such as sea, rivers, lakes, groundwater, drinking water basin, and so forth have been under the threat of different kinds of pollutants by their accidentally and/or intentionally release into waters by industrial and commercial establishments or domestic waste. Among these pollutants, heavy metals which are the important industrial resources and widely used in medicine, metallurgy, chemical engineering, fertilizer industry, etc. are one of the severest contaminations due to its high toxicity



Scheme 1 (**a**) Schematic representation of cellulose-based hydrogel network, (**b**) addition of cellulose-based hydrogel in polluted water having several toxic contaminants such as heavy metals, dyes, pesticides, etc. (I), removal of toxic pollutants by adsorption process using cellulose-based hydrogels (II)

and non-biodegradable structure. Heavy metals can accumulate in living organisms through the food chain and cause serious health problem in the human body even at low concentration in the environment [38–40]. Therefore, the removal of heavy metals from the industrial and domestic effluents is crucial for community health and the environment. Plenty of methods have been employed so far for the removal of heavy metals from wastewater or aqueous solutions containing heavy metal ions such as ion exchange, chemical precipitation, reverse osmosis, flotation, chemical oxidation/reduction, electrochemical techniques, membrane separation, ultrafiltration and adsorption [41–43], etc. Among these methods, adsorption comes into prominence by the advantage of its flexibility in design, reversible nature for multiple uses, high-quality treatment, existing lots of commercially available adsorbents, and simple approach in terms of operational use. An ideal adsorbent for the adsorption of pollutants should simply have some major requirements: (1) inexpensiveness, (2) good mechanical and structural endurance, (3) high adsorption capacity, (4) large surface area, and (5) regeneration [44]. In Fig. 1, required properties of an ideal adsorbent are given for the removal of toxic pollutants from waters.

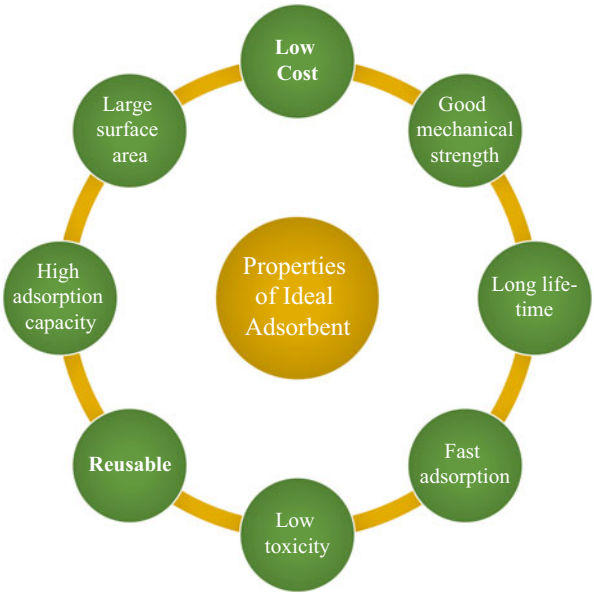


Fig. 1 Required properties of an ideal adsorbent for water remediation

A large variety of materials have been used as adsorbents up-to-date such as clay [45], zeolite [46]-activated carbon [47], chitosan [38], and other polymeric materials [48, 49].

In comparison to the materials mentioned above, hydrogels are considered as promising materials for the effective removal of metal ions from aqueous solutions for the environmental purpose. Hydrogels are three-dimensional cross-linked hydrophilic network materials that can absorb and desorb a large amount of water, and they generally have porous structure and high surface area which are favorable spaces for the adsorption process [50]. When the hydrogels absorb water, they also uptake the water-soluble species and hold them inside their structure. This phenomenon is an excellent feature of the hydrogels which can be used for the wastewater treatment and the removal of heavy metal ions from the aqueous solutions. Heavy metals can create coordination complexes with electron-rich atoms such as oxygen, nitrogen, sulfur, etc. Therefore, hydrogels having electron-rich atoms in their backbone structure possess excellent property for heavy metals to have suitable places in order to form a chelate, and the removal of heavy metals from aqueous solutions can be operated effectively by hydrogels [40]. To constitute such hydrogels, biopolymers are challenging materials than synthetic ones due to their outstanding biocompatibility and biodegradation [51]. As a natural biopolymer, cellulose is the most abundant, versatile, inexpensive, renewable, and widely studied polymer which is usually used for paper industries, fabrics, packaging, binders, and adhesives. Cellulose-based hydrogels have great attraction in the adsorption of heavy metals from aqueous solutions by combining the feature of cellulose and hydrogels' network structure such as possibility of the incorporation of different functional groups that are capable of chelating like hydroxyl, amine, carboxyl, phosphate, etc.,

internal porous structure, high surface area, cost-effectivity, and eco-friendly construction [43, 52]. However, natural polymer-based hydrogels generally have low mechanical strength than the hydrogels based on synthetic polymers. For this reason, scientists' attention is driven to create composite hydrogels using natural and synthetic polymers or inorganic clays and the chemical modification of the natural polymers to obtain superior hydrogel networks [53]. Chemical modification of cellulose can improve the heavy metal adsorption capacity by introducing suitable functional groups into cellulose. Hydrogels composed of modificated cellulose have higher adsorption capacity than unmodified cellulose-based hydrogels for heavy metal ions [41].

A great deal of research on cellulose-based hydrogels owing to their promising advantages has been applied for the removal of heavy metals from aqueous solutions. A study for the removal of heavy metal ions from aqueous solutions was accomplished using chitosan-carboxymethylated cellulose hydrogel [54]. Carboxymethyl cellulose (CMC) which is a derivative of cellulose is a well-known, inexpensive cellulose ether with biodegradable feature. It composed of an anionic linear polymer in which hydrogen atoms of cellulose hydroxyl groups are interchanged by carboxymethyl group. CMC is an excellent natural polymer owing to its anionic groups which is ready to collect counterions such as toxic heavy metal ions in aqueous solutions. Chitosan has also amine and hydroxyl groups in its structure as chelating zone for heavy metal ions. Blending both chitosan and highly carboxymethylated cellulose by irradiation technique to form chitosan-CMC physical hydrogels combines the properties of two natural polymers to increase the heavy metal adsorption capacity from aqueous solution. Radiation cross-linking is the best alternative synthesis approach for such hydrogels instead of using toxic chemical cross-linkers by the advantage of free additive process and high purity product generation. Water swelling of chitosan-CMC hydrogels decreases by increasing chitosan content in the hydrogel structure due to increasing cross-linking degree. However, when the swelling degree of chitosan-CMC hydrogel decreases by the increment of chitosan content, metal (Cu^{2+}, Cd^{2+}, Zn^{2+}) adsorption from aqueous solution increases due to the increase of amino groups on chitosan and cross-linking which provides denser arrangements of functional groups (carboxyl, amino) for chelation in the network. Three possible mechanisms were offered for the adsorption of the divalent metal ions: (1) the adsorption by ionic interaction between each divalent metal ions and one carboxyl group of CMC, (2) the adsorption of each divalent metal ion by two or more carboxyl groups through chelation, and (3) the chelation of divalent metal ions with amino groups of chitosan content. Furthermore, adsorption capacity of the cellulose-based hydrogel significantly increases at higher initial Cu^{2+} concentrations. The adsorption of Cu^{2+} ions at lower concentrations increases linearly, indicating that hydrogel surface has enough active units for adsorption and the level of adsorption depends on the amount of Cu^{2+} that were moved from solution to sample surface.

Another nanocomposite hydrogel based on cellulose was synthesized by grafting method using carboxymethyl cellulose (CMC), *N*-isopropyl acrylamide (NIPAm), and acrylic acid (AA) [55]. Researchers took advantages of the carboxymethyl group

of CMC to collect heavy metal ions and NIPAm which can show great changes in pH, ionic strength, or temperature of the environment to prepare stimuli-responsive hydrogels. Adding nanoscale materials to create a layer inside the hydrogel structure is another approach to improve the mechanical strength and thermal stability of the cellulose-based hydrogels. Graft copolymerization of NIPAm and AA on CMC was carried out in Na-montmorillonite (MMT)/water suspension media which provides the mechanical and thermal strength to obtain hydrogel for the removal of Cu^{2+} and Pb^{2+} ions from water. Swelling degree of the hydrogels increases by increasing pH values which provides the ability of taking more metal ions inside the network structure. High amount of metal ion adsorption by hydrogels was observed, and in the presence of MMT, there was a slight increase compared to the pure hydrogel. Metal ion adsorption capacity of the cellulose-based hydrogels higher for Cu^{2+} than Pb^{2+} ions and pseudo-second-order kinetic model well fitted with the adsorption mechanism. Also, CMC-based hydrogels are selective for Cu^{2+} than Pb^{2+} ions. For nanocomposite hydrogels, two main mechanisms were suggested: (1) adsorption of metal ions by carboxyl groups on the CMC polymer and (2) ion exchange feature of MMT. Cation exchange capacity of the clays as MMT is effective in the removal of heavy metals. The ability of cation exchange of MMT plays an important role in the adsorption capacity of CMC-based nanocomposite hydrogels.

CMC have been mostly used by researchers to prepare hydrogels for the removal of heavy metal ions. Epichlorohydrin (ECH) is a common cross-linker which can react with the hydroxyl groups of CMC in alkaline conditions. Yang et al. prepared CMC-based hydrogel beads using ECH as a cross-linker in aqueous alkaline conditions for the removal of Pb^{2+}, Ni^{2+}, and Cu^{2+} [56]. The cross-linking between CMC and ECH destroyed the crystalline regions of the CMC and increased the amorphous zones in the CMC/ECH hydrogel beads regarding X-ray diffraction measurements understood by disappearing characteristic diffraction signals of CMC. This situation leads to easy penetration of metal ions because of the reducing crystallinity of CMC/ECH hydrogel beads and demonstrates positive impact on adsorption of heavy metal ions. CMC/ECH hydrogel beads have porous structure due to the numerous carboxylate anions which expand the pore sizes of the hydrogel beads by electrostatic repulsions between the carboxylate anions in the hydrogels. Because of the porous structure of the CMC/ECH hydrogel beads, metal ions could easily diffuse into the hydrogel network that could increase the adsorption capacity of the CMC-based hydrogels. SEM photograph proved that the size of the hydrogel's opened pores reduces after the loading of heavy metal ions by diminishing the electrostatic repulsions of carboxylate anions in the network due to the captured cationic metal ions by carboxyl groups.

pH values of the metal ion solutions could affect the adsorption capacity of the hydrogels. When the pH values increase to the alkaline region, the carboxyl groups of CMC/ECH hydrogel beads turn into carboxylate ions (COO^-) which have better electrostatic affinity to the heavy metal ions than carboxyl groups. Therefore, when pH value of the metal ion solution becomes higher than 4.6, the pKa of the carboxylic groups leads the hydrogel highly ionized and results to higher heavy metal adsorption. Amounts of adsorbed heavy metal ions are 6.23, 3.02, and

4.82 mmol/g for Cu^{2+}, Ni^{2+}, and Pb^{2+}, respectively. Cu^{2+} ions are more adsorbed than the others because of the stronger attraction to the lone pair of electrons in the oxygen atoms of carboxyl groups, which leads to prompt more stable complexes with CMC/ECH hydrogel beads.

2-Acrylamido-2-methyl propane sulfonic acid (AMPS) which has electron donor atoms such as N, O, and S that have the ability to form coordinate bonds with heavy metal ions was copolymerized and cross-linked with carboxymethyl cellulose applying γ-irradiation method. Several CMC/AMPS hydrogels with different compositions were synthesized using versatile irradiation dose to generate composite hydrogel for the removal of Co^{2+}, Cu^{2+}, Fe^{3+}, and Mn^{2+} from aqueous solutions. The increase of the AMPS content in the hydrogel causes better cross-linked structure for the absorption of water and the adsorption of the metal ions. However, the increase in the irradiation dose may result the cleavage of CMC chains which leads to lose cross-linked network structure. The synthesized copolymer hydrogels have the following order of affinity for the metal ions, $Fe^{3+}>Cu^{2+}>Co^{2+}>Mn^{2+}$, and can be used at least five times without losing their efficiency [57]. pH is a critical factor for the adsorption process which can affect the chelation of metal ions with the hydrogel's functional groups and swelling properties of the networks. The adsorption of heavy metals typically depends on the pH values, which the adsorption capacity of the CMC/AMPS hydrogels increases when the pH values become higher than pKa values of AMPS. Generally, adsorption of heavy metals on CMC/AMPS hydrogel increases when the pH moves from 1 to 5. At lower pH values, excess of hydrogen atoms competes with metal ions to bind active sites of the hydrogel that causes lower metal ion uptake. The heavy metal ion adsorption of CMC/AMPS hydrogels mainly depends on the content of AMPS inside the hydrogel structure. The increase of the AMPS content stimulates the higher heavy metal adsorption of the hydrogel as well as the increase in pH values and initial metal ion concentration.

Cellulose can be used to improve mechanical strength of the hydrogels and as a binding substrate for heavy metal ions. Collagen which is an animal protein was blended with cellulose to form collagen/cellulose hydrogels for the removal of Cu^{2+} ions from wastewaters [58]. Hydrogen bond interactions between cellulose and collagen units could be increased Young's modulus and tensile strength to provide more robust hydrogels. Composition of the hydrogel affects the surface area of collagen/cellulose hydrogels, which reaches its higher level when the collagen/cellulose hydrogel ratio becomes 2/1. Mainly, amine groups on collagen units were responsible to capture Cu^{2+} ions by chelation, and the maximum Cu^{2+} adsorption capacity of the collagen/cellulose (2/1) hydrogels is 1.06 mmol/g.

In many researches, combining two or more polymers has took place for improving the adsorption properties of the hydrogels. Chitosan-cellulose-based hydrogels have been prepared by an instantaneous gelation method with carboxylated cellulose nanofibril, polyvinyl alcohol (PVA) blended chitosan, and amine-functionalized magnetite nanoparticles, for the removal of Pb^{2+} from aqueous solutions [59]. Carboxylated cellulose nanofibrils (CCNFs) were used as a reinforcing material by their excellent mechanical strength, dispersion stability, and ability to form nanosize networks. Magnetite nanoparticles were introduced into the hydrogel structure for

recycling manner which is promising system to clean up environmental problems. Prepared magnetite hydrogel has better Pb^{2+} adsorption at higher pH values (pH >5.5) due to the OH^- ion concentrations in the adsorption medium. At lower pH values, hydrogel demonstrates lower adsorption because of the competition between H^+ and Pb^{2+} ions. The metal ion adsorption capacity of the hydrogels containing CCNFs is higher than those hydrogels without CCNFs regarding carboxylate groups on the backbone of CCNFs which is playing an important role on adsorption. m-CS/PVA/CCNF hydrogels show quite higher Pb^{2+} adsorption by the value of 171.0 mg/g, and the adsorption capacity can stay at 90% even after four recycling processes.

Graphene oxide (GO) and cellulose were cross-linked using ECH in NaOH/urea aqueous solution to create hydrogels for the heavy metal ion adsorption applications [43]. GO improves the mechanical strength as well as the adsorption capacity of GO/cellulose hydrogels. GO/cellulose hydrogels demonstrate 94.34 mg/g Cu^{2+} uptake capacity which was more than pure cellulose. The GO/cellulose hydrogel also has high adsorption capacity for Zn^{2+}, Fe^{3+}, and Pb^{2+} ions.

Different amounts of PVA and CMC were cross-linked using freeze-thaw method to have composite hydrogels for the removal of heavy metal ions from aqueous solutions [60]. Adsorption studies of obtained porous PVA/CMC hydrogels were conducting for Ag^+, Ni^{2+}, Cu^{2+}, and Zn^{2+} in noncompetitive and competitive conditions. The highest adsorption capacity was observed by P2C1 (containing two-thirds of PVA and one-third of CMC) hydrogel toward Ag^+ ions. PVA/CMC hydrogels show higher selectivity to Ag^+ than other heavy metal ions. Ni^{2+} possesses lower adsorption due to the weaker attraction between Ni^{2+} and functional groups of PVA/CMC hydrogels.

Acrylic acid was grafted on cellulose to obtain cross-linked C-g-AA hydrogels using *N*,*N*′-methylene bisacrylamide (MBA) as a cross-linker for Cu^{2+} and Ni^{2+} removal from aqueous solutions [41]. The adsorption capacity of C-g-AA hydrogels increased by increasing the initial metal concentrations and the pH value of the solution. Maximum adsorption capacity of C-g-AA hydrogels was found as 182 and 200 mg/g for Cu^{2+} and Ni^{2+}, respectively.

A composite hydrogel using both natural polymer sugarcane bagasse cellulose (CB) and gelatin (GT) by incorporation into the copolymer network which comprise of acrylamide (AM) and acrylic acid (AA) cross-linked with MBA [53]. Experimental results revealed that an increase in the GT or CB content enhanced the adsorption capacity of the hydrogels. An increase in the amount of AM/AA causes a reduction in the adsorption capacity. The adsorption mechanism of the optimized hydrogel was confirmed as chemisorption of Cu^{2+} to the hydrogel by second-order kinetics.

Sodium carboxymethyl cellulose (CMC-Na) and sodium styrene sulfonate (SSS) were cross-linked by γ-irradiation to form a hydrogel for the removal of heavy metal ions from contaminated waters [61]. Water uptake ability of the CMC/SSS hydrogels is higher than CMC hydrogel due to the -COOH and $-SO_3H$ groups on the polymer backbone, and also adsorption of metal ions was becoming more effective with these functional groups.

Table 4 Removal of heavy metals by cellulose-based hydrogels

Sample	Heavy metals	Adsorption capacity	References
CMC hydrogel	Cu^{2+}	~230 mg/g	[62]
CPGTCB	Cu^{2+}	49.1 mg/g	[53]
m-chitosan/PVA/CCNFs	Pb^{2+}	171.0 mg/g	[59]
CMCh/PAN hydrogels	Cu^{2+} Co^{2+} Cd^{2+}	4.659 ppm 3.981 ppm 4.095 ppm	[63]
CMC/AMPS (CAM 6)	Co^{2+} Cu^{2+} Fe^{3+}	60.6 mg/g 75.3 mg/g 80.4 mg/g	[57]
CMC/chitosan physical hydrogels	Cu^{2+}	169.49 mg/g	[54]
CCHB3	Cu^{2+}	1.06 mmol/g	[58]
Chitin/cellulose (3:1)	Hg^{2+} Cu^{2+} Pb^{2+}	2.30 mmol/g 1.75 mmol/g 2.20 mmol/g	[64]
Cellulose	Hg^{2+} Cu^{2+} Pb^{2+}	0.7 mmol/g 0.25 mmol/g 0.75 mmol/g	[64]

Generally cellulose have been used after modification or combined with other natural or synthetic polymeric materials to create hydrogels for the removal of toxic heavy metal ions. A consolidated overview of cellulose-based hydrogels for heavy metal adsorption has been given in Table 4. CMC is prompted as one of the most used cellulose derivatives to obtain cellulose-based hydrogels for the removal of heavy metal ions from aqueous solutions. Moreover, cellulose-based hydrogels have been studied by synthesizing as composite gels mainly using organic or inorganic nanofillers to improve their metal binding capacity and mechanical strength.

4.2 Removal of Dyes

Since ancient times, humanity have used pigments for artistic and decorative purposes [65]. These pigments were obtained from plants, insects, animals, and minerals. With the development of industrial process since the nineteenth century, natural dyes left its place to synthetic dyes which have reduced the cost and facilitate to produce them [66].

Dyes have been extensively used (about 7×10^5 ton per year [67, 68]) in many industries including textiles, food, plastics, paper, leather, pharmaceutical, etc. Among them, textile industries are the main pollution factor for water resources which they are responsible for 20% of total water pollution in the world according to the World Bank report [69]. Dye pollution in wastewater affects marine life negatively by inhibiting penetration of sunlight and reduces the dissolved oxygen (DO) level in water.

All dyes are toxic, carcinogenic, and mutagenic, even at low concentrations; therefore the existence of dye in the environment could cause health problems to human beings and aquatic living organisms [70]. Moreover, dyes in wastewater have become crucial issue because they have high chemical oxygen demand, strong color, high toxicity, poor biodegradability, and persistent bioaccumulation [71]. Due to their negative effects into the environments, dye pollution must be solved immediately.

Dye removal from wastewater can be achieved by three main process, including physical separation, chemical process, and biological degradation. Different methods such as electrocoagulation [72–74], oxidation [75], membrane separation [76, 77], and adsorption [78–81] have been mostly used for the removal of such dyes from wastewater. Although each method has advantages and disadvantages, adsorption has been known to be mostly used in the effective process because of its low cost, effectiveness, ease of use, and environmentally friendliness [82].

Although activated carbon is the most used material for the removal of dyes from wastewater, however, its high costs, nonreusable, and low efficiency restrict its use as sorbents. An ideal adsorbent should have some criteria such as easily accessible, fast sorption rate, high absorption capacity, reusable, and low cost. One way to obtain good and effective sorbents for the removal of these kinds of pollutants from water is to prepare cross-linked hydrogel. Considering the abovementioned criteria, cellulose-based polymers have gaining much interest, and many efforts have been also conducted to investigate the cellulose-based materials as sorbent for the removal of dyes from wastewater.

For example, Zhang et al. have prepared an adsorbent using acrylic acid and carboxymethyl cellulose as dye removal material. The dye removal efficiency was investigated using methyl orange, disperse blue 2BLN, and green chloride and was found to be 84.2%, 79.6%, and 99.9%, respectively [83].

Salama et al. have synthesized a superabsorbent hydrogel using carboxymethyl cellulose and 2-(dimethylamino) ethyl methacrylate. The effect of contact time, pH of solution, and initial dye concentration on the adsorption of methyl orange onto cellulose hydrogel were studied, and the maximum adsorption capacity was reported to be 1825 mg for 1 g of superabsorbent hydrogel [67].

Mahdavinia et al. [84] have produced nanocomposite hydrogels from grafting of acrylamide onto hydroxypropyl methylcellulose (HPMC) with the incorporation of the natural sodium montmorillonite. The final nanocomposite hydrogels were used for the removal of cationic crystal violet from wastewater, and the maximum adsorption capacity of nanocomposite hydrogels is 67.2 mg/g.

Deng et al. [85] prepared novel high-strength and highly cost-effective hydrogel using chitosan and cellulose. The obtained material showed good elasticity, high strength, excellent resilience, and high interest toward Congo red. It was found that the saturated adsorption amount was found to be 166.10 mg/g of hydrogel. It was also found that the removal rate was ≈100% when the initial concentration was less than 100 mg/L.

A nanocomposite hydrogel containing lignocellulose-g-poly(acrylic acid), MMT has been utilized as adsorbent for the removal of methylene blue (MB) from aqueous solution. The effect of MMT content, contact time, initial concentration and pH of

the dye solution, and adsorption temperature were investigated. It was found that the adsorption capacity of MB increased with the increasing contact time, initial dye concentration, and pH value but decreased with increasing MMT content and temperature. The maximum capacity of obtained hydrogels was reported as 1994.38 mg/g for methylene blue [86].

Juang et al. [87] have used cellulose-based wastes and banana and orange peels, for the adsorption of different dyes including methyl orange (MO), methylene blue (MB), rhodamine B (RB), Congo red (CR), methyl violet (MV), and amino black 10B (AB) from wastewater. It was found that the banana peel was more effective than the orange peel. The amount of adsorption for banana peel was found to be 17.2 for MO, 15.9 for MB, 13.2 for RB, 11.2 for CR, 7.9 for MV, and 7.9 mg/g for AB under the conditions tested ($C_0 = 100$ mg/L, dosage of adsorbent 1 g/L).

Varaprasad et al. [88] used carboxymethyl cellulose (CMC) together with acrylamide (AM) and graphene oxide (GO) for the design of hydrogel via free-radical polymerization method to obtain cross-linked structures. The CMC-AM-GO hydrogels were used to adsorb dye from an acid blue 113 solution, and the removal capacity of hydrogels was reported as 185.45 mg/g.

Novel interpenetrating polymer networks (IPNs) were prepared by the copolymerization of cellulose, polymethacrylic acid (PMAA), and bentonite as a dye adsorbent. *N*,*N*′-methylenebisacrylamide (MBA) and potassium peroxydisulfate ($K_2S_2O_8$) were also used as a cross-linker and an initiator, respectively. It was found that the hybrid hydrogels can be reusable for the removal of MB with the capacity of 371.67 mg/g [89].

Tam et al. investigated the preparation of hydrogel beads comprising of cellulose nanocrystals and the alginate [90]. The effect of various parameters including adsorbent dosage, pH, temperature, ionic strength, contact time, cross-linking ratio, and bead size on the dye removal efficiency was investigated. The maximum capacity was found as 256.41 mg for a gram of hydrogel beads.

Wang et al. [91] developed a low-cost bio-adsorbent by mixing corn stover hemicellulose with polyethylene glycol diglycidyl ether under alkaline conditions, and also clay nanosheets have been used to prepare hybrid hydrogels. The synthesized materials were investigated for the adsorption of methylene blue. The adsorption capacity of hydrogels with and without clay was 148.8 and 95.6 mg/g, respectively. It was found that the addition of clay into the prepared material improved both mechanical strength and the adsorption capacity of hydrogels.

Liu et al. [92] synthesized a cellulose-based adsorbent via free-radical polymerization methods. The adsorption kinetics (pseudo-first-order, pseudo-second-order, and intraparticle diffusion models) was also studied, and the maximum adsorption capacity of sorbent was reported as 1734.816 mg/g at pH 9.

Atrei et al. reported [93] the preparation of magnetic hydrogels based on carboxymethyl cellulose using magnetite nanoparticles functionalized with 3-aminopropyltrimethoxysilane as a cross-linker. The developed hydrogels were investigated as adsorbents for organic and inorganic pollutions including methylene blue and cadmium chloride and found to be 620 ± 100 mg/g for methylene blue and Cd (100 ± 15 mg/g), respectively.

A novel adsorbent was prepared via cross-linking graft copolymerization of 2-dimethylamino) ethyl methacrylate (DMAEMA) onto the carboxymethyl cellulose backbone. The synthesized hydrogels are used to adsorb methyl orange from wastewater, and its capacity is 1825 mg for 1 g of hydrogels [67].

Yao et al. synthesized an eco-friendly porous cellulose-based bio-adsorbent by grafting of acrylic acid and acrylamide, and the final adsorbents were used to remove acid blue 93 (AB93) and methylene blue from single and binary dye solutions. The effects of initial dye concentration, adsorbent dosage, contact time, pH value of solution, temperature, ionic strength, and surfactant amount on the dye adsorption capacity of the prepared material were investigated. The maximum adsorption capacities for AB93 and MB were 1372 mg/g of adsorbents (initial concentration, 2500 mg/L) [94]. Table 5 summarizes the adsorption capacities of the cellulose-based hydrogels.

Table 5 Adsorption capacities of the cellulose-based hydrogels

Materials	Dye	Initial concentration (mg/L)	pH	Adsorption capacity (mg/g)	Ref.
Nanocomposite hydrogel	Crystal violet	30	10.0	67.2	[84]
CMC-AA adsorbent	Malachite green chloride	30	7.0	147.9	[83]
Hemicellulose/clay hybrid hydrogels	Methylene blue	200	5.0	148.8	[91]
Pineapple peel cellulose-based hydrogels	Methylene blue	100	7.0	153.85	[95]
Chitosan/cellulose hydrogel	Congo red	500	–	166.1	[85]
CMC-AM-GO-based hydrogels	Acid blue 133	100	6.0	185.45	[88]
Cellulose nanocrystal-alginate hydrogel beads	Methylene blue	100	7.0	256.41	[90]
Interpenetrating polymer network	Methylene blue	1000	6.5	317.17	[89]
Carboxymethyl cellulose hydrogels	Methylene blue	–	7.0	620	[93]
Macroporous cellulose-based cryogels	Methyl blue	200	8.0	990.1	[96]
Cellulose-based bio-adsorbent	Acid blue 93 Methylene blue	2500	9.0	1372	[94]
Cellulose-based porous adsorbent	Methylene blue	3000	9.0	1734.82	[92]
CMC-based superabsorbent hydrogel	Methyl orange	1500	3.0	1825	[67]
Lignocellulose-based nanocomposite hydrogel	Methylene blue	2500	10.0	1994.38	[86]

4.3 Removal of Other Pollutants

Cellulose-based hydrogels have been used mainly to remove toxic heavy metal and dyes from waters. Matter such as oil, pesticides, bacteria, drug, etc. are other contaminants for water resources that can cause serious water pollution and affect human health. Cellulose-based hydrogels were involved for the removal of those kinds of pollutants as well as heavy metals and dyes from waters.

Organic pollutions such as pesticides, petroleum products, and polyaromatic hydrocarbons (PAHs) have toxic, carcinogenic, and mutagenic features for human life [97]. For this reason, the removal of such pollutants is highly essential. Adsorption is the most commonly used technique to remove different kinds of organic pollutants including PAHs, pesticides, oils, etc. [98, 99]. Despite having restricted studies of cellulose-based hydrogels for other pollutants, several scientific works are summarized in this section.

Ghaffar et al. produced carboxymethyl cellulose hydrogels by copolymerization of acrylamide and methacrylic acid onto carboxymethyl cellulose via direct radiation grafting technique [100]. It was shown that the obtained polymeric hydrogels have interest not only toward dyes and heavy metals but also toward pesticides such as 4-chlorophenol and 2,4-dichlorophenoxy acetic acid. The adsorption capacity of carboxymethyl cellulose hydrogels for 4-chlorophenol and 2,4-dichlorophenoxy acetic acid is reported as ≈6 and ≈14 g/g, respectively.

Mattaso et al. fabricated polyacrylamide- and methylcellulose-based hydrogels as an adsorbent for the removal of pesticide paraquat from aqueous solution [101]. The maximum adsorption capacity was found to be 14.3 mg/g for the obtained hydrogels.

Berry et al. synthesized biodegradable ethanethiol-cellulose bead hydrogels by a novel method using 1,1′-carbonyldiimidazole followed by the reaction with aminoethanethiol [102]. The adsorption of metolachlor from aqueous solution was examined batch reaction conditions and fixed-bed column technique. The maximum adsorption capacity of cellulose beads was found to be 1300 μmol/g metolachlor.

Cellulose-based hydrogels were prepared from carboxymethyl cellulose sodium salt and β-cyclodextrin [103]. The swelling capacities in water were 70–200 mL/g of hydrogel beads. It is also found that the prepared hydrogel beads have also interest toward bisphenol A (BPA) in water. Batch adsorption experiments were analyzed using Langmuir isotherm models, and the maximum BPA adsorption capacity of polymer hydrogels was 167 μmol g^{-1}.

Nano-fibrillated cellulose (NFC) hydrogel was used to modify a hydrated regular cellulose filter for the separation of oil from waters [104]. NFC was cross-linked using citric acid to add stability and strength to the coating, avoiding breakdown of the coating during filtration process and providing long lifetime for filter. Hydrated regular cellulose is modified by dipping and drying process using NFC which creates a hydration layer over regular cellulose by absorbing water. Oleophobic behavior of modified cellulose filter was improved by triple layer of hydrogel, water, and oil. The high difference surface energy between water and oil keeps the oil away from penetrating through filter. Without the modification of filter by NFC hydrogels, both water and oil could penetrate through filter and cause fouling and clogging.

NFC hydrogel creates a hydrated layer when it reaches maximum swelling degree and provides a big surface energy difference between oil and filter. Modified filter prevents the oil clogging inside filter by the help of NFC hydrogels and permits the flow of water while repels the oil penetration. Cellulose-based hydrogel was used in a nanoscopic scale to improve an eco-friendly water/oil separation method.

5 Conclusion

This chapter summarizes the recent progress in the application of cellulose-based hydrogels for water treatments. With the increasing industrializations, population growth, urbanization, and technological improvements worldwide, water pollution from heavy metals, dyes, oils, and other organic contaminants has become a significant problem for human life and animals even at very low concentrations. Aquatic pollutants such as heavy metals, dyes, oils, etc. are very dangerous pollutants which once enter the water make water no longer safe for drinking purposes, and removal of organic pollution from wastewater is very important from the point of view of the environment and health. Various approaches such as membrane separation, oxidation, reverse osmosis, etc. have been utilized for the removal of aquatic pollutions. Among them, adsorption has gained importance for the removal of such pollutants from wastewater due to their fascinating properties such as low cost, reusability, and high and quick adsorption abilities.

Cellulose-based hydrogels have many favorable properties such as hydrophilicity, biodegradability, biocompatibility, thermal and chemical stability for water treatment applications, low cost, and nontoxicity. Therefore, cellulose-based hydrogels have wide application in many areas including sensors, tissue engineering, drug delivery, agriculture, and water purification. Several reports have indicated that cellulose-based hydrogels are considered to be an ideal material for the removal of different inorganic or organic pollutants such as heavy metals, organic solvents/oils, antibiotics, dyes, and other contaminants. With ongoing research in cellulose-based hydrogels, the properties of cellulose-based materials will be much better and applicable than in current form, and cellulose which is environmentally friendly and low cost will replace with the petroleum-based materials.

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Cellulose-Based Hydrogels for Agricultures

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Abstract

The cellulose-based hydrogel characteristics such as biodegradability and biocompatibility mark its suitability toward agriculture application. In agriculture, the hydrogels are specifically used as water reservoirs, phytopharmaceuticals (protected cultivations, soilless cultivations, and open-field cultivations), pesticide release, and nutrient release to the soil. The hydrogels are impregnated by fertilizer components (e.g., soluble phosphate, potassium ions, nitrogen compounds), and those chemicals which are trapped in a polymer network cannot be immediately washed out by water but gradually released into the soil and then absorbed by plants. The hydrogels are classified as two classes, i.e., soluble and insoluble hydrogels. The soluble variety is used to reduce irrigation erosion in fields. The insoluble variety is used in gardens, nurseries, and landscapes to reduce frequency of watering. They are produced either in the form of powder or of a bulky material with a well-defined shape and a strong memory of its shape after swelling. The material can be charged with small molecules, such as nutrients, to be released under a controlled kinetic. The main advantage is controlled release of water, longtime maintaining soil humidity, increase of soil porosity, and therefore better oxygenation of plant roots. The agricultural hydrogel behavior depends on various factors such as temperature, relative humidity, soil type, stress, etc. The performance of the gels is evaluated through different techniques like moisture retention, nutrition release rate, biodegradation rate, relative humidity, and temperature maintained in the soil. Several studies reveal that the amount of moisture retained in the soil is dependent on the concentration of the cellulose-based superabsorbent matrices. Those SAPs/hydrogels were used in specific agriculture application such as nutrient release, conservation of land, and drought stress reduction due to several advantages. The advantage of cellulose-based hydrogels include eco-friendliness, high water holding capacity, low cost, and biodegradability. Moreover, their application helps reduce irrigation water consumption, causes lower death rate of plants, improves fertilizer retention in soil, and increases plant growth rate.

Keywords

Moisture retention · Fertilizer · Drought stress · Biodegradation

1 Introduction

Hydrogel agriculture technology was introduced in the late 1980s; it involves the formation of polymer gels using insoluble water-absorbing polymers [1]. The agricultural hydrogels are referred to as water retention granules because they swell to many times their original size when they come in contact with water [2].

The hydrogels used in agriculture can absorb between 400 and 1500 grams of water for every gram of hydrogel [3], and similarly, they can release the absorbed water. The speed of water absorption and release depends on the type of hydrogels used. The volume transitions – absorbing and releasing water – depend on the external stimuli which can be physical (temperature, electric or magnetic field, light, pressure, and sound) or chemical (pH, solvent composition, ionic strength, and molecular species) [4–9].

Globally, the water resource crisis exists; therefore, future food demand for rapidly increasing population pressures is likely to further aggravate the effects of drought [10]. The severity of drought is unpredictable as it depends on many factors such as occurrence and distribution of rainfall, evaporative demands, and moisture-storing capacity of soils [11]. Hence, water-saving agriculture is found essential for sustainable development of human societies [12]. Therefore, the hydrogels came into use to save water and prevent land erosion. The hydrogels have emerged as an alternative to the current needs for the agriculture sector; the most important agricultural areas are gardening, horticulture, and silviculture [13]. Several cellulose-based hydrogels are used in agriculture sectors; mostly the polysaccharides based, including those of complex structures, such as pectin [14], cashew gum [15], Arabic gum [16], starch [17], chitosan [18], chitin [19], and so on, are used for agriculture application. Johnson and Veltkamo's report also stated that when these hydrogels are used correctly, 95% of their stored water is available for plant absorption [20].

In addition, the hydrogels also act as a nutritive system, i.e., the hydrogels uptake some nutrient elements, hold them tightly, and release the absorbed nutrient elements in a controlled way; thereby the plant takes in the fertilizers and helps for improved growth [21, 22]. These benefits are easily noticed in nurseries and seedling beds, crops sensitive to moisture stress, crops requiring large quantities of water, and container gardens – pot cultures, etc.

Furthermore, agricultural hydrogels have tremendous potential to improve physicochemical and biological properties of the soil [23]. The cellulose-based hydrogels are capable for use in all crops and all soil types, as they are eco-friendly and naturally degraded over a period of time, without leaving any toxic residue in the soil and crop products. Thus, this chapter focused on detail discussion on the significance, characteristics, and different cellulose-based hydrogels used in specific application of agriculture. Moreover, the benefits in utilization of hydrogels in the agriculture application are detailed.

2 Categories of Cellulose-Based Agricultural Hydrogels

Cellulose-based hydrogels such as alginate, starch, and chitosan and the cellulose ether-based hydrogels are widely used in agriculture application. The gels are prepared with the use of cross-linkers; for cellulose, mostly epichlorohydrin,

aldehydes, aldehyde-based reagents, urea derivatives, carbodiimides, and multifunctional carboxylic acids are used as cross-linking agents. The cross-linking reactions between the cellulose chains are activated by chemical agents and may occur in water solution, in organic solvents, or even in the dry state [24–27]. These cellulose and its derivative-based gels have high potential toward water absorption and retention. In particular, cellulose-based hydrogels obtained from nontoxic cross-linking agents [25, 28] are attractive for agriculture application.

2.1 Carboxymethyl Cellulose (CMC)-Based Hydrogels

CMC is produced from cellulose where the raw material is wood or cotton linters. As it is known that cellulose is not water soluble, CMC is made water soluble as a result of a chemical reaction between cellulose and monochloroacetic acid (MCA) in the presence of sodium hydroxide [29]. The polar carboxyl groups on the backbone of CMC render the cellulose to be soluble, chemically reactive, and strong chelating compounds, making it suitable for water absorption. Among all cellulose ethers, only carboxymethyl cellulose (CMC), available as sodium salt CMC-Na, is a polyelectrolyte, and it is considered as smart cellulose derivative which shows sensitivity to pH and ionic strength variations, plus good swelling capability [30]. Sannino and co-workers [31] have also developed and patented a novel class of cellulose-based polyelectrolyte hydrogels, totally biodegradable and biocompatible, whose swelling capability can be modulated by adjusting several synthesis parameters [32, 33] and was more suitable for agriculture application. Likewise, Xiao et al. have also developed biodegradable cellulose-based hydrogels from CMC and cellulose cross-linked with nontoxic polyethylene glycol diglycidyl ether (PEGDE) [34]. The swelling behavior of the hydrogels was studied by changing the cross-linker concentration and the ratio of CMC to cellulose. The higher amount of hydrophilic CMC in the hydrogel had shown higher swelling ratio. Similarly, Ibrahim et al. [35] have prepared also superabsorbent hydrogels from carboxymethyl cellulose by copolymerization with acrylamide initiated by electron-beam irradiation. These cellulosic water absorbents are widely accepted around the world, because of their economic advantages and environmental amiability.

Further, the CMC-based gels are also used in control release of pesticides. Li et al. developed the controlled-release formulations of acetochlor, which had shown higher safety to the user and nontarget organisms. Moreover, they had shown wide reduction of the herbicide application rates and leaching in soils [36]. Their study used CMC gel and different types of clays, to develop the controlled-release formulations of herbicide acetochlor. They also evaluated the performance of inorganic clays in dried gel formulations on slowing the release of acetochlor and related to their sorption capacities, while the organic clay did not lead to the slowest release. In addition, according to the parameters of an empirical equation which were used by the author to fit the herbicide release rate, the release of acetochlor from clay/CMC gel formulations was controlled by diffusion mechanism as reported in Sect. 4.2.

2.2 Hydroxyethyl Cellulose (HEC)-Based Hydrogels

According to the literature, the hydroxyethyl cellulose (HEC) is used along with CMC-Na to develop the hydrogel and is used in many agriculture applications, particularly for storing water. Because the CMC cannot be used as itself reported in the literature [37], it tends to form intramolecular rather than intermolecular cross-links. Demitri et al. developed CMC-Na/HEC hydrogels cross-linked by means of a water-soluble carbodiimide, for the sustainable release of water (and nutrients) to plant root [25]. Seki et al. prepared hydrogels using a mixture of CMC-Na and HEC with fumaric acid (FA) and malic acid (MA) as a cross-linker [38]. The author reported that CMC-Na/HEC hydrogels containing MA as a cross-linker have shown greater water uptake capacity than CMC-Na/HEC hydrogels containing FA as a cross-linker. Montesano et al. developed hydrogel using sodium carboxymethyl cellulose (CMC-Na) and hydroxyethyl cellulose (HEC), with citric acid as cross-linking agent. Their results showed beneficial effects on water retention properties of a sandy soil and perlite (soilless substrate) and are suitable for potential use in agriculture, especially for short-growing cycle crops [39].

2.3 Cellulose-Alginate-Based Hydrogel

Alginate is a natural polysaccharide having mannuronic and glucuronic acid remains and calcium ion cross-linking. Cross-linking can be observed at room temperature and physiological pH. The controlled releases of solute on soils are carried out from many types of chemically cross-linked hydrogels. The release of nutrients from alginate microparticles, achieved by spraying a solution of sodium alginate into an aqueous solution of calcium chloride, can be transformed by coating the particles [40]. Alginate-based hydrogels are used for controlled release of nitrogen, sulfur, and oxygen (NSO) [41]; a sodium alginate-glutaraldehyde-cross-linked hydrogel has been investigated as a matrix for natural liquid pesticide neem seed oil [42]. A starch-alginate-clay composite was also used for the release of a fungicide thiram [43]. Similarly, microspheres of sodium alginate/starch cross-linked with Ca^{2+} have been used as a controlled-release matrix for the release of the pesticide chlorpyrifos [44].

2.4 Cellulose-Starch-Based Hydrogels

Starch is a widely used polysaccharide for hydrogel and most abundantly available. The polysaccharides are used in hydrogel field as a constituent key, serving as a support on polymer network and allowing other properties such as biodegradability [45]. In other words, if the polysaccharide chains break, the hydrogel unmakes. This characteristic makes the polysaccharide-based hydrogels appropriate for uses

in soils as a fully biodegradable system for controlled release of nutrients, as they are susceptible to biodegradation by microorganisms [46]. The cellulose/starch blends are used to produce superabsorbent hydrogels; initially the starch is dissolved into water to form gel-like solution and then modified with cellulose. Fekete et al. synthesized carboxymethyl cellulose/starch superabsorbent hydrogels by gamma irradiation. Hydrogels were also synthesized only with carboxymethyl starch and carboxymethyl cellulose in the presence of MBA cross-linker [47, 48]. There is no information available about the possible applicability of carboxymethyl cellulose/starch blends for superabsorbent. But the literature reveals that the rate of biodegradation increases with the introduction of starch into the complex structure or cellulose ethers [49]. It is also noted that starch-based gels are potential candidates to improve the soil properties, mainly in conditions of reducing moisture availability. Other authors investigated the applicability of the polymers; common hydrogels and superabsorbent improve the soil properties [50–52]. Parvathy et al. [53] studied the effect of superabsorbent hydrogel based on saponified cassava starch-g-poly(acrylamide) on the physical-chemical and biological properties of soil. They also investigated the effect of the same hydrogel on the growth parameters of chili (*Capsicum annuum* L.) in different irrigation intervals. The results showed that the amount of moisture retained in the soil was dependent on the concentration of superabsorbent matrices, which provides a better control of release of adsorbed water. Starch/ethylene glycol-*co*-methacrylic acid hydrogel was designed for the controlled release of pesticides like fluometuron, thiophanate, thiophanate methyl, and trifluralin [54].

2.5 Cellulose-Chitosan-Based Hydrogels

Chitosan-based hydrogels are prepared by cross-linking of the polymer with glycerol phosphate disodium salt; mostly, they are used for drug delivery; these gels are rarely adapted for agriculture application. The chitosan solutions maintain liquid state below room temperature in the presence of salt, where they promptly become gel under heating. Siepmann et al. synthesized carboxymethyl-hexanoyl chitosan with desirable swelling properties which is used as a drug carrier for amphiphatic agents [55]. Their study reported that these hydrogels had both hydrophilic (carboxymethyl) and hydrophobic (hexanoyl) moieties, but the hydrophobic part retarded the de-swelling process, causing better water retention properties.

3 Significance of Hydrogels for Agriculture Application

- Agricultural hydrogels are not only used for water saving in irrigation, but they also have tremendous potential to improve physicochemical and biological properties of the soil. They potentially influence soil wealth, viz., permeability, density, structure, evaporation, and infiltration rates of water [2].

- Agricultural hydrogels help to save water by reducing the irrigation frequency; it acts as soil condition and thus helps to overcome the drought conditions.
- Agricultural hydrogels are eco-friendly, because they are naturally degraded over a period of time, without leaving any toxic residue in the soil and crop products. They help to increase the agricultural production with sustainability in water-stressed environment.
- Agricultural hydrogels form a consistent cyclic process of absorption and release of water; the water so released can provide optimum moisture for quick germination and seedling maturation. Thus, it reduces seedling mortality by several folds in nurseries.
- Agricultural hydrogels reduce overuse of fertilizers and pesticides in fields. The chemicals absorbed with water by the hydrogels are released in a controlled way or slowly, thus extending the natural life through enhancing the efficacy of the root systems [56].
- In cold regions, death during germination and maturation is common due to moisture freezing in and around plant root tissue. Absorbed moisture in hydrogels does not freeze and makes easy accessibility to plants. It also regulates seedling growth temperature preventing death by freezing.
- Agricultural hydrogels act as soil matter flocculants. They closely bind loose soil, thus forming loams that can help better root latching. Simultaneously, the repeated absorb-release mechanism prevents over-compaction of soil minerals and provides space for aeration and development of soil edaphon.
- Agricultural hydrogel can be used for all crops and all soil types. Its benefits are most easily noticed in nurseries and seedling beds, crops sensitive to moisture stress, crops requiring large quantities of water, and container gardens – pot cultures [23].
- It has a wide area of application ranging from agriculture, forestry, industrial planting, municipal gardening, drought management, to water conservation. It helps reduce soil erosion by surface runoffs and fertilizer and pesticide leaching to groundwater, reducing cost of water and irrigation and success rate at growth and high yields of crops.

4 Performance Evaluation of Agricultural Hydrogels

The overall performance of agricultural hydrogel depends on various factors such as type of polymer, manufacturing process, and environmental and soil condition. The constraints like fragile structure of hydrogels particularly at higher temperatures, high rate of biodegradability, and reduced water absorption capacity under practical use situations have restricted their promotion and use in agriculture. Therefore, mainly the parameters considered for evaluating performance in case of agricultural hydrogels are moisture content present in the soil, rate of nutrient release, relative humidity of soil, temperature maintained in the soil, and the biodegradation rate of hydrogel, shown in Fig. 1.

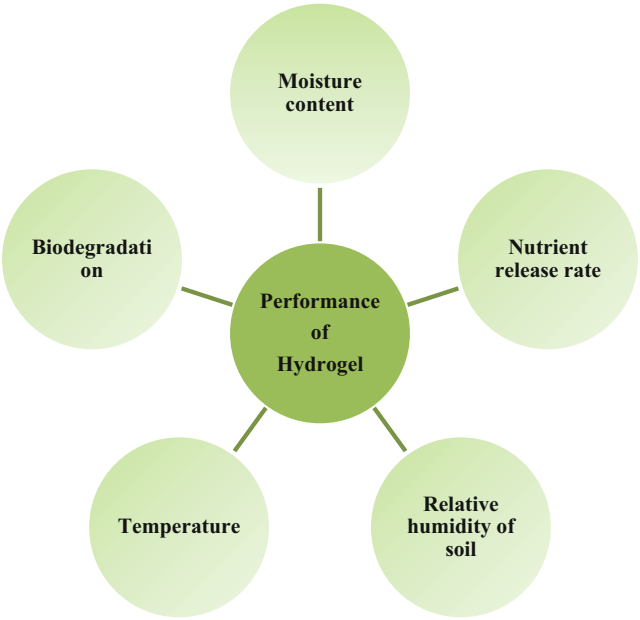

Fig. 1 Factors affecting performance of agricultural hydrogels

4.1 Rate of Moisture Content

The percentage of soil moisture varies based on the efficiency of hydrogels. The effect of the hydrogel on moisture release to soil is determined by simple gravimetric method. In general, the soil moisture content is expressed by weight as the ratio of the mass of water present to the dry weight of the soil sample or by volume as ratio of volume of water to the total volume of the soil sample.

Initially, a known quantity of soil is brought to 0% moisture by drying the soil at a temperature of 105 °C for a period of 12 h. Then, a known amount of water is added in small increments. The percentage of moisture in soil is calculated using Eq. (1) [57]:

$$\%\text{of water in soil} = \frac{\text{Total weight of water added}}{\text{Weight of dry soil sample}} \times 100 \tag{1}$$

In addition to the traditional technique, the degree of moisture is also determined using soil master moisture meter. Gilbert et al. (2014) studied the effects of hydrogels on soil moisture and growth of *Cajanus cajan* in semiarid zone. Their study found that the hydrogels increased soil moisture in the soil, so they are recommended for use in semiarid lands to boost the survival and growth of seedlings [58]. Similarly,

several researchers evaluated the effects of hydrogel and compost on soil moisture retention capacity [59–61]. Besides the nature of hydrogels and soils, the degree of soil moisture varies with many factors such as vegetation, slope, weather condition, soil characteristics, etc. [62].

4.2 Rate of Nutrient Release

Studies reported that slow- and controlled-release behavior of fertilizers is ideal for sustainable growth of plant. Controlled or slow nutrient releases are achieved through special chemical and physical characteristics. These characteristics depend on the manufacturing methods and the type of fertilizers that are used to prepare polymeric hydrogel. Commonly, urea, ammonium sulfate, and ammonium chloride are used as fertilizers, and their release rates are accessed from nitrogen content [63]. According to Ni et al., a predetermined quantity of coated hydrogels are sealed in plastic mesh bags and kept at a particular depth below the surface of the soil at ambient temperature. The soil moisture retained as 20% throughout the test and then at a regular interval of time; the mesh bags are retrieved and placed in a paper bag and air-dried [64]. Then, the granules in the mesh bags are assessed for nitrogen content. Furthermore, as demonstrated by author Al-zahrani [65], the release rate of nitrogen from different fertilizer substrates in soil is analyzed using mathematical models as shown below (2,3) [64]:

$$\frac{M_t}{M_0} = 6(1+\alpha)\left(\frac{tD}{\pi R^2}\right)^{0.5} \tag{2}$$

$$\alpha = \frac{C\infty}{C_0 - C\infty} \tag{3}$$

where M_t/M_0 is the ratio of active ingredient released at time t, D is the diffusion coefficient, R is the radius of the fertilizer granule, C_0 is the initial concentration of the fertilizer, and C_∞ is the concentration of the fertilizer in the sphere at infinite time.

Many researchers have also prepared and evaluated the hydrogel efficiency in fertilizer delivery [66, 67]. Abed et al.'s study prepared the hydroxyethyl cellulose (HEC)/NPK fertilizer and followed biological experiments for evaluating the release rate of fertilizers. Initially, the polymeric fertilizers are mixed with dry soil and incubated at laboratory conditions for particular period; and then a determined quantity of seeds are planted in pots. Finally, the pots are irrigated to field capacity (once every 3 days) for a period of 30 days and evaluated percentage of seed germination and weight of plant shoot part. Similarly, Chatzoudis et al. determined the water-soluble potassium leaching percentage to dry soil, and their study has confirmed that the presence of hydrogels in soil increased dissolution of controlled-release fertilizers [68].

4.3 Relative Humidity of Soil

Relative humidity (RH) is the ratio of actual water vapor content to the saturated water vapor content at a given temperature and pressure expressed in percentage (%). RH directly influences the water relations of plant and indirectly affects leaf growth, photosynthesis, pollination, occurrence of diseases, and finally the total yield. When RH is low, transpiration increases causing water deficits in the plant. Water deficits cause partial or full closure of stomata and increase mesophyll resistance blocking entry of carbon dioxide. When RH is high, the evapotranspiration reduces and influences the translocation of nutrients hence suppressing the yield. Therefore, optimal humidity with adequate soil moisture favors would be beneficial for agriculture.

The research-grade sensors are used to find the total humidity of the soil [69]. To determine the humid content, different amounts or concentrations of the hydrogel were mixed with the soil, and the soil without the amendment of the hydrogel was used as the control. Then, the soil was watered and the humidity content was measured using sensors. Many researchers constantly monitored humidity content through custom-made sensors; the data acquired was useful in determining the optimal time point to irrigate the soil [70, 71].

4.4 Effect of Temperature

Temperature changes affect important hydraulic characteristics of compacted clays including water retention and permeability; any small variation can lead to very significant changes in saturation time [72]. The variation in the swelling with respect to the temperature is determined using a simple experiment. Initially, the prepared hydrogel of predetermined quantity is weighed and placed in different beakers. One beaker was left with the water at room temperature 25 °C, and the remaining are heated to a particular temperature and maintained. Then, the difference in the percentage of swelling with respect to the temperature was calculated using Eq. (4):

$$\mathrm{SR}_{(t)} = \mathrm{TW}_{(t)}/\mathrm{TW}_{(A)} \times 100 \tag{4}$$

where $\mathrm{SR}_{(t)}$, percentage of swelling ratio with respect to temperature; $\mathrm{TW}_{(t)}$, total weight at elevated temperature; and $\mathrm{TW}_{(A)}$, total weight at ambient temperature.

Many authors reported that the various factors affect the rate and amount of water absorption. Peng et al. have also measured the equilibrium swelling ratio of hydroxyethyl cellulose-based hydrogels in buffer solution with pH 7.0 at varying temperature range from 25.0 °C to 45.0 °C [73]. Similarly, Li et al. also developed the hydrogel from hydroxypropyl cellulose by copolymerizing with N-isopropylacrylamide; their study reported that the manufactured hydrogels were temperature sensitive [36]. According to the study of Saeed et al., significant increase in the swelling ratio was found with elevated temperature. The large quantity of water which was penetrated into internal structure of hydrogel bead was the result of increased entropy of solution, which in turn increased the diffusion process [74].

4.5 Rate of Biodegradation

The superabsorbent hydrogels prepared from cellulose and its derived materials will have unanimous properties such as nontoxicity, high absorbency, salt resistance, etc. and are highly own to biocompatibility and biodegradability as they are renewable. Cross-linked hydrogels are susceptible to degradation by cellulase enzyme and by the action of microorganisms in compost or under natural conditions in soil; those hydrogels are considered under the group of biodegradable materials [75]. Tomsic et al.'s [76] study revealed that cellulose-based hydrogels are degradable by several bacteria and fungi present in air, water, and soil, in other words the ability of the material to be digested or metabolized by microorganisms [77].

The biodegradation behavior of hydrogel is evaluated by simple experiments. Initially, a determined quantity of hydrogels are enclosed in a lidless plastic bottle, and the bottle was left in a pit, with a slope of 45°, and opened downward, and then the setup is buried in the soil. After a period of 3 months, the bottle was taken and weighed. The degree of biodegradation is calculated using Eq. (5):

$$\text{Percentage of biodegradation} = \frac{W_0 - W_1}{W_1} \times 100 \tag{5}$$

where W_0 and W_1 were the wet weights of the hydrogel in the bottle before and after degradation.

Studies have confirmed that hydrogel is sensitive to the action of UV rays and degrades into oligomers. The cellulose and its derivative-based hydrogels are more sensitive to aerobic and anaerobic microbiological degradation and can degrade by releasing water, carbon dioxide, and nitrogen compounds as by-products. The hydrogel molecules are too voluminous to be absorbed into plant tissue; they have zero bioaccumulation potential. Orozco et al. assessed the hydrogel degradation chemistry and kinetics in the soil; the preliminary results have shown that the degradation occurs over a period of approximately 6 months without significantly altering the soil chemistry. Further, their study reported that the gels could be recycled and used as a reservoir in agriculture [78].

5 Key Characteristics of Agricultural Hydrogels

Cellulose-based agricultural hydrogels are natural polymers; they can absorb a minimum of 400 times of their dry weight of pure water and gradually release it according to the needs of the crop plant. The hydrogels swell-dry-swell multiple times based on the external environmental condition. They are capable to perform well at temperatures 40–50 °C and hence are suitable for semiarid and arid regions [23]. The rate of absorption is not much necessary for agricultural hydrogels; instead they should have high absorbency under load (AUL) [79]. They were highly durable and stable in the swelling environment and during storage.

Generally, the hydrogels are pH sensitive, and their swelling capacity varies based on the pH level. The agricultural hydrogels should have lowest sensitivity toward salinity. The swelling under salinity is revealed through a known relationship as given below:

$$\text{Swelling} = k[\text{salt}]^{-n}$$

where k and n are constant values for an individual superabsorbent. The k value is swelling at a high concentration of salt, and n value is a measure of salt sensitivity.

The water-absorbing polymers exist with neutralization; hence, they do not affect nutrient availability, soil chemical composition, and action of other agrochemicals, viz., fertilizers, herbicides, fungicides, insecticides, etc. Hydrogels improve the physical properties of soils such as porosity, bulk density, water holding capacity, soil permeability, infiltration rate, etc. It also increases biological/microbial activities in the soil, which increase oxygen/air availability in root zone of the plant [1]. The cellulose-based hydrogels used in agriculture application are environmentally friendly and low cost and gradually biodegrade without the formation of toxic species.

6 Specific Applications of Agricultural Hydrogel

6.1 Nutrient Release

The nutrients commonly used in agriculture are classified as macronutrients and micronutrients [80]. The micronutrients (N, P, K, Ca, Mg, and S) are those that require in high contents for plant physical structure, and macronutrients (B, Cl, Co, Cu, Fe, Mn, Mo, Ni, and Zn) are those that require in low contents for different plant growth stages such as germination, root growth, and leaf force [81]. In order to deliver the required nutrient to the plants in correct time, the agricultural hydrogels are used. Agricultural hydrogels for release of nutrient are synthesized by impregnation fertilizer components (e.g., soluble phosphate, potassium ions, and nitrogen compounds) [82]. Chemicals trapped in a polymer network are immediately washed out by water but gradually released into the soil and then absorbed by plants.

In other words, as shown in Fig. 2, semipermeable polymer coating surrounds a water-soluble fertilizer. Water penetrates the coating and dissolves the fertilizer inside the prill increasing the osmotic pressure, which in turn increases the size of the coat's micropores. Then, fertilizer solution then exits the substance through the coating pores into the substrate. The simplest way to use superabsorbents in agriculture is their mixing with the soil. The effectiveness of the process depends on the soil properties such as aeration, temperature and nutrient transport, and water uptake and transformation. Cellulose-based hydrogels are recommended for the controlled release of water and nutrients in arid and desert areas. Many technology based approaches such as (i) encapsulated soluble fertilizers, (ii) low-solubility inorganic salts, (iii) low-solubility organic compounds, (iv) slowly degraded organic materials Shaviv and his co-workers followed release the soluble nutrients in a controlled way

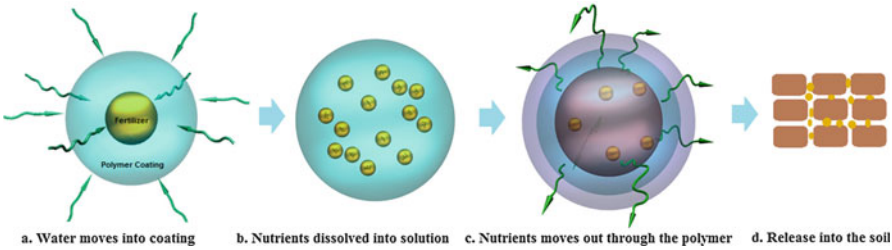

Fig. 2 Schematic representation of controlled release of fertilizers absorbing water and releasing it to soil

[83]. The study report of Liu et al. stated that the combination of slow-release fertilizers and superabsorbent polymers may improve the nutrition of plants, mitigate the environmental impact from water-soluble fertilizers, reduce water evaporation losses, and lower the frequency of irrigation [36].

Cellulose and its derivatives have been used to synthesize novel superabsorbent hydrogels. Studies reveal that cellulose derivative-based hydrogels are commonly used to increase the efficiency of pesticides and herbicides using lower doses and to indirectly protect the environment by reducing pollution and cleaning up existing pollutants [33]. The utilization of synthetic fertilizers is also greatly reduced when hydrogel agriculture is practiced without hindering the crop yield and nutritional value. Wu et al. synthesized chitosan-coated nitrogen, phosphorus, and potassium (NPK) compound fertilizer and studied the controlled-release and water-retention properties [21]. Their study prepared hydrogel compound with the water-soluble NPK as core region, the chitosan as inner coating, and the poly(acrylic acid-co-acrylamide) (P (AA-co-AM)) as outer coating. The compound resulted not only with controlled-release property but also high water absorption which helped to preserve the soil moisture. Similarly, Noppakundilograt et al. also synthesized novel cross-linked tri-layered NPK fertilizer hydrogels using poly(vinyl alcohol) and chitosan [84]. Guilherme et al. have also developed pectin-based polymer hydrogel to the release of phosphate, potassium, and urea. In their study, the release process of fertilizers from the hydrogels was controlled by non-Fickian mechanism with a tendency of macromolecular relaxation [85]. The cellulose-based hydrogels are majorly used for nutrient release as they offer several advantages such as controlled release of water, longtime maintaining soil humidity, increase of soil porosity, and thereby better oxygenation of plant roots.

6.2 Conservation in Agricultural Lands

In the last few decades, the land degradation seems to be a major issue all over the world. The degradation of lands is the fact of degradation of organic soil matters. In addition, the climatic changes have also resulted with dry lands (e.g., desertification), which reduced the soil productivity and soil water availability [86].

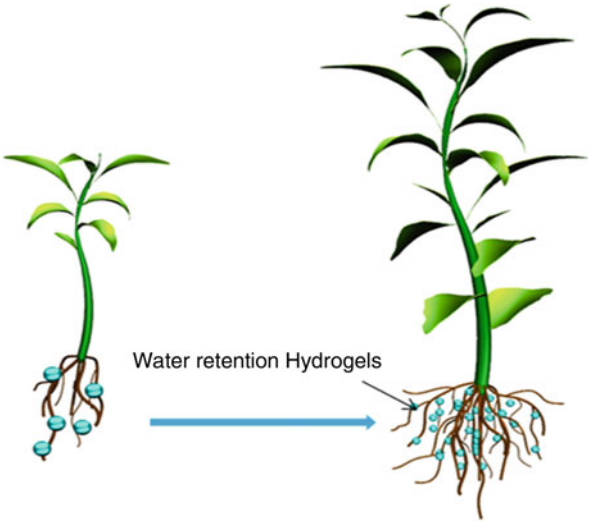

Fig. 3 Conserves agriculture lands: Reserves moisture to roots and soil

Water stress due to scarcity of moisture around root zones caused serious impacts in agriculture such as premature leaf shedding, decreasing chlorophyll content, reduced seed yield, less fruit and flower yield, etc. To moderate the deficit irrigation, it is necessary to use water-retaining agent; therefore, a promising technology was adapted by the researchers and scientists, i.e., the application superabsorbent polymers (SAPs) to these soils. The utilization of SAPs fundamentally reduces the frequent watering to trees/plants. Once the trees or plants are established, the root systems go deeper and continue feeding the tree/plant as shown in Fig. 3.

The SAPs are like artificial humus as they are hydrophilic and contain carboxylic groups. This enables them to bind cations and water [87]. Al-Humaid and Moftah stated that the hydrogels are successfully used in agriculture as soil increased its water content [88]. Nnadi et al. developed a cross-linked carboxymethyl cellulose (CMC) and starch-based hydrogel and evaluated its performance on water-retaining capacity and rate of irrigation [49]. Their study found that the addition of hydrogel polymer increased the water retention capacity of soil by 50–70% with proper amendment with various dosages of soil to hydrogel ratio. The hydrogel is found to have direct influence on soil permeability, density, structure, texture, evaporation, and infiltration rates of water. Cannazza et al.'s study also confirmed that the presence of the SAP had a beneficial effect in hindering water evaporation phenomena and in providing a higher quantity of water over a longer period of time [89]. Basuki et al. synthesized soil conditioner-based hydrogels using graft copolymerization of chitosan-acrylamide; their study has shown that the hydrogels have maintained better physicochemical properties of soil [18]. Barbucci et al.'s [90] study also revealed that the superabsorbents increase the water retention of soils when they are used as soil additives; in addition, they also replace peat and aid for traditional moisture retention of soil [91]. Apart from the water retention capacity, the utilization of hydrogels could offer several advantages such as enabling the

plants to survive longer, inducing higher growth rate in plants, reducing the rate of evapotranspiration, reducing the water consumption in agriculture, etc. Further, they help to bind heavy metals and mitigate their action on plants. They can also mitigate the effects of salinity and promote the microbial actions in soil.

6.3 Drought Stress Reduction

Drought can be defined as the absence of rainfall or irrigation for a period of time sufficient to deplete soil moisture and cause dehydration in plant tissues. Drought stress can lead to production of oxygen radicals that result in increased lipid peri-oxidation and oxidative stress in the plants. The drought stresses affect multiple physiological parameters such as reduction in the size of leaf, stem extension, and root proliferation. Further, they also disturb the plant water relations and reduce water-use efficiency on plants [92]. The schematic representations of drought stress reduction, improvement on quality of soil, and plant growth stimulation are shown in Fig. 4.

Tudela and Primo-Millo's studies confirmed that the citrus plant had severe leaf injuries and were even wilting under drought condition [93]. The reason behind was insufficient CO_2 assimilation by leaves mainly by stomatal closure, membrane damage, and disturbed activity of various enzymes, especially those of CO_2 fixation and adenosine triphosphate synthesis [94]. Severe water stress may result in the arrest of photosynthesis, the disturbance of metabolism, and finally the death of plant [95]. The reactions of plants to water stress differ significantly at various organizational levels depending upon intensity and duration of stress as well as plant species and its stage of growth [95, 96].

The effects of water stress on plants are reduced by the utilization of hydrogels. The water absorbed by a hydrogel (superabsorbent polymer) withstands and extends

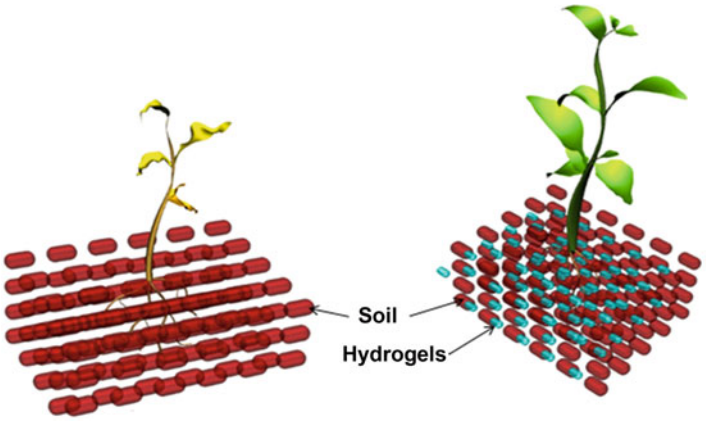

Fig. 4 Drought stress reduction: Improves quality of soil and stimulates plant growth

the moisture to the soil at different levels of depths as required by the plants/crops, which in turn relieves the water stresses. Further, the hydrogel modified the soil water retention properties. The soil moisture at field capacity was almost increased with the highest percentage of 400% compared to the not amended soil. According to the study of Montesano et al., the plants grown in the presence of hydrogel, subjected to a controlled water stress, showed a greater hydration of leaf tissue.

Cannazza et al. developed cellulose derivative-based chemically cross-linked SAP and evaluated its performance especially the water absorption/desorption cycles in the soil for cultivation of plants [89]. The study found to have many advantages with the use of SAP such as controlled release of water, longtime maintenance of soil humidity, increase of soil porosity, and better oxygenation of plant roots. Satriani et al. have also demonstrated the importance of biodegradable cellulose-based superabsorbent polymers in the management of water irrigation systems in bean crop cultivations in areas affected by water scarcity. Their study confirmed that the SAP hydrogel maintained good water potential in the drought stress and at the same time reduced the irrigation water consumption [97].

7 Conclusion

This chapter has discussed the various cellulose and its derivative-based gels used in agriculture application. Generally, a wide range of cellulose-derived hydrogels are used for agriculture; particularly the gels obtained from nontoxic cross-linking agents are focused by the researchers as they produce safe and ecological crops. In this chapter, cellulose derivative hydrogels, namely, the CMC and HEC, have been detailed; in addition, the blends of cellulose with other natural polymers such as alginate, starch, and chitosan are also discussed. The performance of these gels varies based on different environments, and their evaluations through simple experiments are also described. In order to evaluate the performance of the hydrogels, various factors such as moisture content, nutrient release rate, temperature, relative humidity, and biodegradation were considered. In addition, the agricultural hydrogel key characteristics and its significance are detailed.

Furthermore, the SAPs/hydrogels used in specific agriculture application such as nutrient release, conservation of land, and drought stress reduction are conferred which induces numerous agro-advantages such as afforestation of degraded lands, soil enrichment, reduction of irrigation water consumption, reduction of death rate of plants or crops, improving fertilizer retention in soil, and increase of plant growth rate.

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Cellulose-Based Hydrogel Films for Food Packaging

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Tabli Ghosh and Vimal Katiyar

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Abstract

The use of fossil-based plastic in food packaging has increased the plastic-based waste, carbon footprint, and global warming, which has led to the development of alternatives such as hydrogels for biodegradable stringent food packaging industries. Hydrogels consist of biopolymers having three dimensional networks can trap a large quantity of water and formulation of cellulose-based hydrogels have laid high impact for food packaging application with improved biodegradability, biocompatibility, mechanical properties, plasticizing effect, etc. Cellulose hydrogels can be imparted as thin layers onto the polymers to improve its wettability, appearance, degradability, and resistance towards environmental agents. Cellulose-based hydrogels are mainly formulated from cellulose, bacterial cellulose, and its derivatives. Further, use of cellulose and its derivatives with gelatin, low-methoxyl pectin, polyvinyl pyrrolidone (PVP), polyvinyl alcohol (PVA), polyethylene glycol (PEG), protein, etc., provide a better property for packaging food products. Various bioactive compounds such as silver nanoparticles and other antioxidants, antifungal agents can be embedded onto hydrogel films to improve its properties. Use of cellulose hydrogel as packaging material mainly depends on its hydrophilicity, swelling property, molecular weight, stability, physical, mechanical and chemical properties. Cellulose hydrogels generally consist of various chemistry of hydrogels such as physical cross-linking, chemical cross-linking, interpenetrating hydrogels, which find significant importance in biodegradable food packaging. Dry hydrogels from biopolymers can be used individually or in conjugate with others. However, use of individual polymers for making hydrogel creates problems in hydration which enhance water-polymer interactions than polymer-polymer interactions. In contrast, blending and composites of polymers help in enhancing interactions between polymer-polymer matrices than water-polymer matrices. The tailored properties of blends or composites of hydrogel can be formed through electrostatic interactions between opposite charges, formation of cross-links through covalent bond, formation of physical networks, and interpenetrating polymer networks.

Keywords

Cellulose · Cellulose derivatives · Hydrogel · Biodegradability · Food packaging

1 Introduction

Food packaging plays a crucial role in day-to-day life of human beings as being used in preserving food products; protecting them from external environmental factors such as unfavorable gaseous conditions, microorganisms, insects; and promoting them for consumerization [1]. Further, packaging provides easy transportation of food stuffs by acting as a safe guard against deterioration caused during transportation. The most commonly used food packaging materials include paper, aluminum foil, paper board, plastic films, metal container, glass and their recycled form, edible films, coatings, and hydrogel [1–9]. Among various available packaging materials, polymer-based packaging materials provide some

advantageous properties over others such as light weight, easy handling, water impermeability, transparent, soft, heat sealability, and others. The conventionally utilized polymers for food packaging include polyethylene (PE), polypropylene (PP), polystyrene (PS), polyvinyl chloride (PVC), poly vinyl acetate (PVAc), ethylene vinyl alcohol (EVOH), and others. The use of these non-biodegradable fossil-based polymers create environment pollution, which increases the carbon footprint in the world thereby diminishing petroleum-based resources (nonrenewable resources) and creating many technical problems during recycling or carbonizing [10]. In this regard, for fulfilling the demand of consumer without harming the environment, biopolymers (bioplastics and biodegradable polymers) are explored for its various applications [11]. The developed biodegradable polymers include polylactic acid (PLA), polyglycolic acid (PGA), polyhydroxyalkanoates (PHA), polyethylene succinate (PES), polycaprolactone (PCL), polypropylene adipate (PPAd), polybutylene succinate (PBS), polybutylene succinate-co-adipate (PBSA), and others, which are chemically or microbial derived polymers from various sources [11–20]. Moreover, agro-based biopolymers including cellulose, lignocellulose, hemicellulose, chitosan, proteins, lipids, and their derivatives along with composites, and their hydrogels can be utilized for making biodegradable packaging materials [21–24]. In concern with the properties of biopolymers in comparison to conventional polymers, biopolymers should deliver all required properties for preserving and protecting the stored food materials. Due to the poor properties of biopolymers in comparison with biomass-based polymers, properties and quality of biopolymers are tailored by various techniques such as blending of biopolymers with conventional polymers, development of polymer biocomposites, combination of biopolymers which is made possible by improving polymer interaction, intermolecular forces, cross-linking within the molecules, etc. [25–27].

Hydrogel-based polymers are defined as a class of polymeric materials having three dimensional network structure and being puffed up with water providing exclusive physical properties [24, 28]. The uniqueness for capturing ample amount of water is observed due to their hydrophilic nature, which helps in creating a wide application in the field of food packaging. However, the hydrogel-based food packaging has a great potential to deliver a new opportunity for developing sustainable and green packaging [29] along with the property of improving the freshness of fruits and vegetables [30]. Though utilization of all biopolymers-based hydrogel in food packaging has not been reported and used, but its beneficial properties such as biocompatibility, nontoxicity, and biodegradability make this class a noticeable entity in the field of food packaging [28]. In addition, hydrogels for food packaging can be prepared individually or with other biopolymers and conventional polymers to design an ideal type of food packaging. Figure 1 shows some of the biopolymers intended for use as a hydrogel-based packaging materials. Further, use of hydrogel provides a new prospect over other packaging forms due to their improved water capturing and mechanical properties along with acting as a proper food packaging material with higher efficacy. Hydrogels are primarily casted to films and dried for tailoring its property [31].

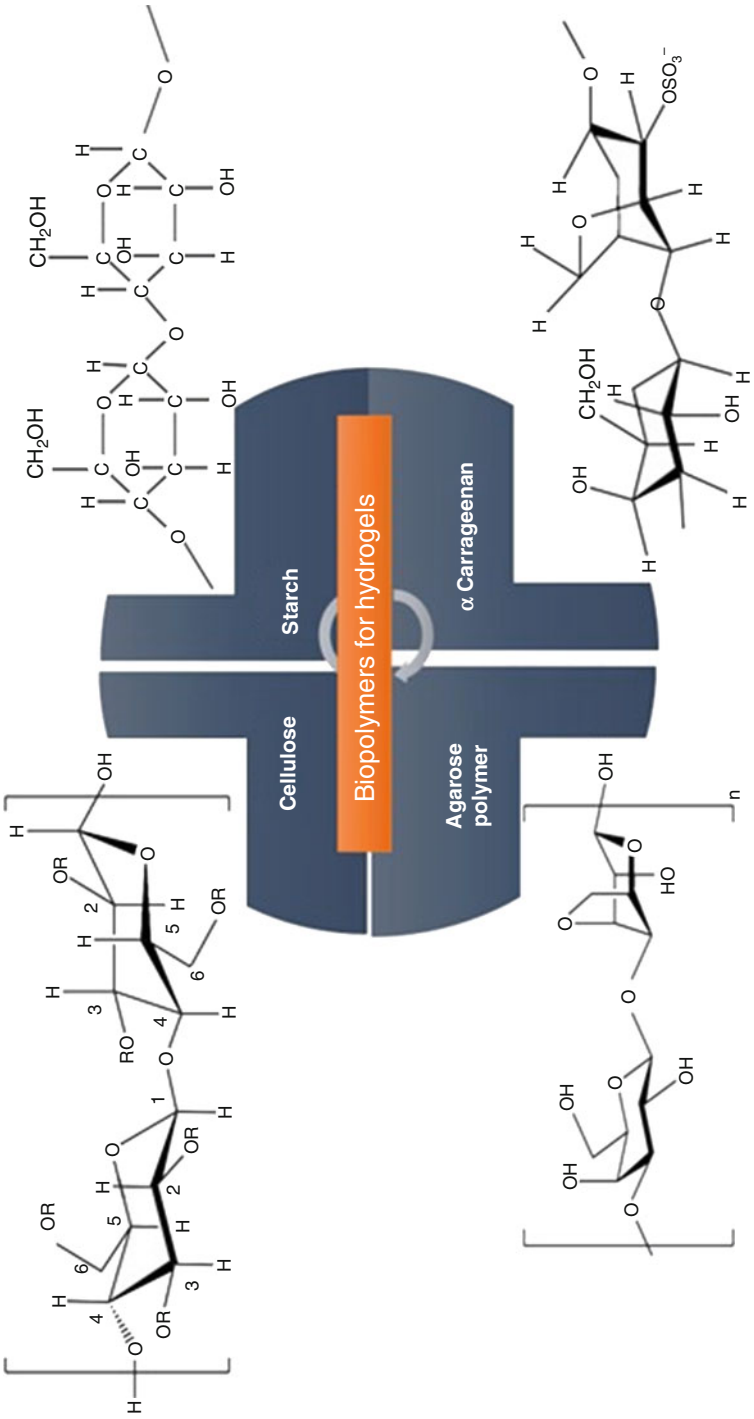

Fig. 1 Biopolymers intended for use as a hydrogel based polymeric material. (Note: Substitution of R groups will provide derivatives of cellulose molecules as detailed: methylcellulose (R: H, CH_3), ethylcellulose (R: H, CH_2CH_3), carboxymethylcellulose (R: H, CH_2COONa), hydroxypropylcellulose (R: H, $[CH_2CH(CH_3)O]_nH$), hydroxyethylmethylcellulose (R: H, CH_3, $[CH_2CH_2O]_nH$))

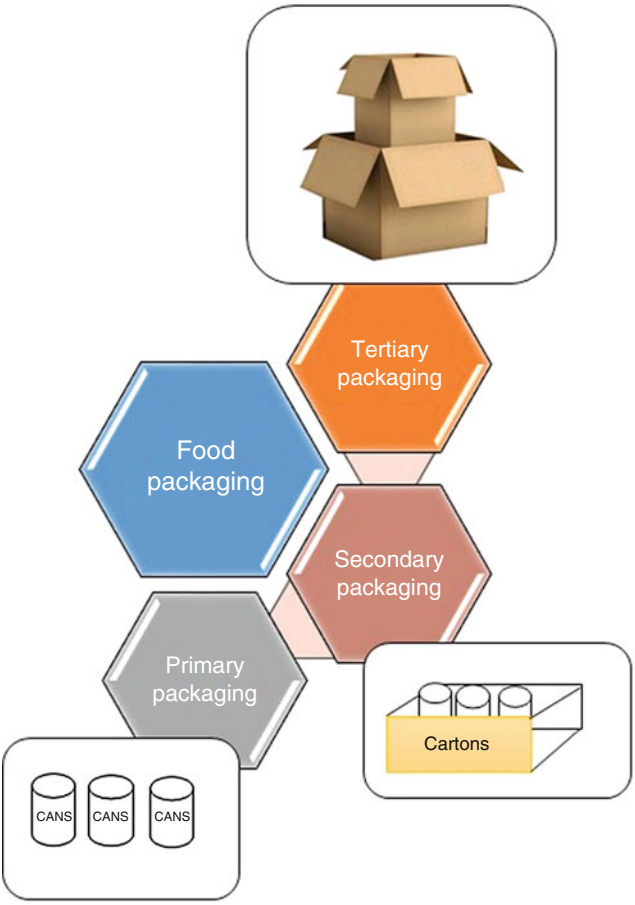

Fig. 2 Classes of packages based on its contact with food material

Moreover, in consideration to contact of food materials to packages, food packaging can be classified into three categories, viz. primary packaging, secondary packaging, and tertiary packaging (Fig. 2) [32]. Primary packaging remains in contact with products, which can directly be purchased by the consumers for consuming purpose; secondary packages are used to carry the primary packages such as boxes, cartons; and tertiary food packaging which contain the large amount of goods for transportation purpose, and also carry the secondary packages. Under all the classes, secondary and tertiary food packaging can be recycled and reused, but primary food packages gets contaminated, which make them unacceptable for reuse and recycle. Noticeably, hydrogel-based packaging materials act as primary packaging materials for food products, which stay in contact with the food products.

Remarkably, over past few days, focus has been shifted to hydrogel-based food packaging due to their water trapping properties [33]. However, shortcomings on the

usage of these hydrogels lie within their swelling and de-swelling property. Considering these limitations, there is a need of more concentrated research to evaluate the hydrogel as food packaging material. Development of polysaccharide-based hydrogels is gaining attention for food packaging. Polysaccharide is a class of carbohydrate mainly consisting of a number of monosaccharide units. Polysaccharide-based biopolymers involve starch, cellulose, chitosan, gums, chitin, and others having an enormous way to develop hydrogel-based food packaging [8, 24, 34, 35]. These kind of biopolymers are generally extracted from renewable resources such as plant materials, fruit waste, shells, waste of insects, extract of plants, microbes, etc. The film forming capability of these biopolymers provide an opportunity towards their use as a food packaging material. Moreover, the strategical techniques need to be formulated to overcome the existing shortcomings such as hydrophilicity (having a tendency to absorb water) due to more polymer-water interaction. Polysaccharide-based polymers have immense prospective for industrially viable approach in the field of stringent food packaging and beverage industry.

Cellulose is one of the superior, well utilized, and widely available polysaccharide-based biopolymers being used to formulate hydrogel for its enormous beneficial properties for acting as a food packaging material [36, 37]. The biopolymer has many beneficial properties such as biodegradability, biocompatibility, nontoxicity, easy availability, which makes it one of the focused and significant biopolymers in human life [38, 39]. The acid-alkali treatment of biomass involves soda pulping and bleaching which yields cellulose and further can be shaped in various forms to be utilized as hydrogels such as powders, films, particles, composites, achieving diverse application in various fields of life [40, 41]. The beneficial properties of Cellulose-based hydrogels provide prospects to replace fossil-based materials in the field of stringent food packaging and food-based industry as stabilizer, additives, thickeners, etc.

Based on the above discussion, this chapter mainly accounts the development and use of cellulose based hydrogels with improved properties which are suitable for food packaging materials. In the beginning, a brief introduction towards available biopolymers for making hydrogel which are intended for utilizing in food packaging materials are demonstrated. In addition, details about cellulose-based hydrogel with other polymers for improved properties has been outlined and different techniques required to characterize the hydrogel for acting as a better food packaging material are detailed. Finally, a detail case study on available cellulose-based hydrogels as food packaging materials and their biodegradation study has been outlined.

2 Biopolymer-Based Hydrogels for Food Packaging Applications

As discussed, various natural biopolymers provide suitable properties for developing dry hydrogel with tailored properties for acting as food packaging materials. Further, this dry hydrogel can be reinforced with bioactive compounds, health beneficial cells, and protectable drugs for improved properties. The bioactive compounds are

well available commercially and can be easily extracted from food-based sources such as (1) spices including ginger, garlic, cardamom; (2) fruits and vegetables including apple peel, sohiong, carrot, guava, papaya, orange, etc., and many other sources. Moreover, bioactive compounds include phenolic, flavonoids, anthocyanin, carotenoids, vitamin C, minerals, and others. Incorporation of active compounds to the films can improve its property in terms of antioxidant, antimicrobial, antibacterial, antihypertensive, anticholestremia, antifungal, etc. [8].

2.1 Cellulose-Based Hydrogels

Nowadays, cellulose, its derivatives, and various forms such as cellulose nanocrystals (CNC), cellulose whiskers, and cellulose fibers are utilized to fabricate hydrogel for various applications. This specific biopolymer can be uniformly applied on the polymer surfaces as thin sheets of deposit to tailor the packaging properties. The available cellulose derivatives as represented in Fig. 1 include methyl cellulose (MC), carboxymethyl cellulose (CMC), hydroxypropyl cellulose (HPC), and hydroxypropylmethyl cellulose (HPMC) [42]. The available derivatives can be combined with other polymeric materials such as gelatin, low-methoxyl pectin, polyvinylpyrrolidone (PVP), polyvinyl alcohol (PVA), polyethylene glycol (PEG), protein, etc. [24, 29], to provide superior properties for packaging food products.

Though use of unmodified form of cellulose in various fields have been extensively studied throughout the world, but presence of functional groups (hydroxyl groups) in it acquires a new prospect for tailoring the properties of hydrogels through the formation of ionic, covalent, complex cross-linking networks, multiple component-based networks (hybrid cross-links), and composite-based networks (blends self-assembling networks) [36]. Further, cellulose is sensitive towards pH, temperature, ionic, electro responses, which in turn imparts a great impact on its usage. On this basis, cellulose-based hydrogels can be developed through reversible gel formations such as polyelectrolyte complexes, interpolymer matrix, hydrophobic associations, and hydrogen bonding as represented in Fig. 3 and cellulose tends to be a perfect material for preparing better water containing materials through various cross-linking networks. Cellulose and its derivatives mixed with other polymeric materials impart improved polymer-polymer interaction over water-polymer interactions to be used in food packaging and industrial applications. In this way, physical cross-linking between cellulose molecules is the primary reason for forming cellulose hydrogels. But, the difficulty in developing cellulose hydrogel is the selection of the appropriate solvent for making the solution as cellulose is not easy to dissolve because of its hydrogen bonding throughout the structural lay out. Although, some solvents such as ionic liquids (ILs), alkali aqueous system, urea (thio urea) aqueous system, N-methylmorpholine-N-oxide (NMMO), LiCl/dimethylacetamide (DMAc) system are lately used to dissolve cellulose for making hydrogels [36]. Moreover, a newer prospect has been made through the use of bacterial cellulose for developing cellulose hydrogel, taking the advantage of specific bacterial species. In addition, various design parameters may affect the property of physical and chemical hydrogel

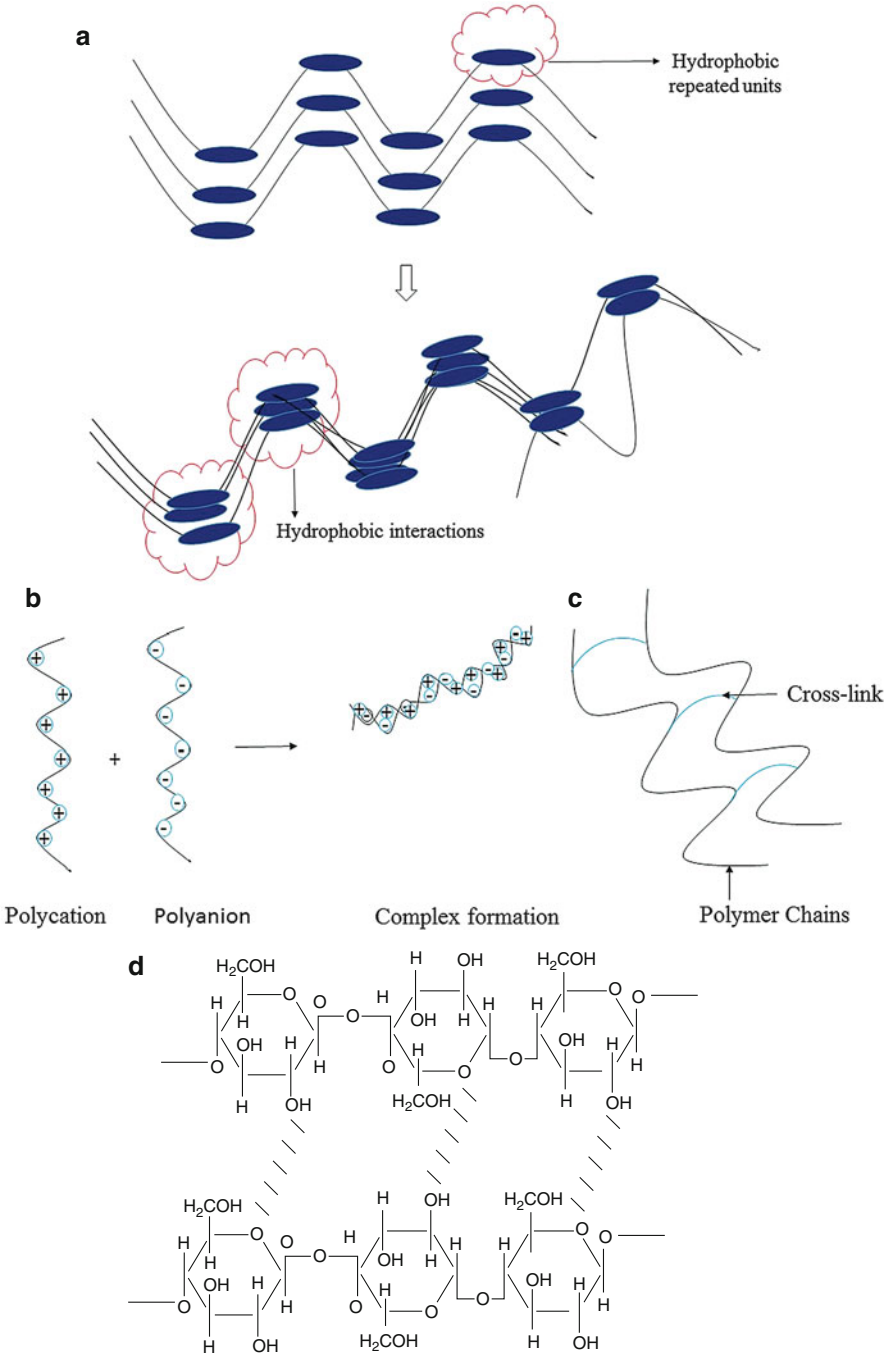

Fig. 3 Mechanism of formation of cellulose-based hydrogels intended for food packaging through (**a**) Hydrophobic interactions; (**b**) Polyion formation; (**c**) Cross-linking within molecules; and (**d**) Hydrogen bonding within the molecules

and formulation of cellulose with other materials that help in improving its properties such as better mechanical properties, biodegradability, biocompatibility, nontoxicity, plasticizing effect, etc. [34].

2.2 Starch-Based Hydrogels

Starch is a class of available renewable polysaccharide, consisting of number of α-glucose unit and can be extracted from cereals, tubers, corns, root, waxy potatoes, and others [43–47]. Further, amylose and amylopectin are the two unit of starch molecule, where amylose contains α (1 → 4) glucose unit and amylopectin consists of α (1 → 4) glucose unit having a branch unit of α (1 → 6) glucose unit [48]. Starch has a potential to act as a film former, which is mainly imparted by amylose molecule. Further, starch-based films are biocompatible, nontoxic, flexible, and oxygen impermeable, which make them a great candidate for acting as a film former in the field of food packaging [24]. On the contrary, this specific biopolymer lacks in efficient mechanical properties, which can be tailored by adding other biopolymers or synthetic polymers without compromising its biodegradability. In addition, modifications in terms of chemical and surface or blending with other polymers or plasticizing materials makes them appropriate for acting as film former materials. However, starch-based hydrogel has not been used yet for using as food packaging. Though the development of starch-based hydrogel with other synthetic polymers intended to put an enormous impact in the field of food packaging industry.

2.3 Agar-Based Hydrogels

Agar is a type of polysaccharide, generally obtained from agarose and agaropectin, where agarose contains upto 70% of the mixture [49]. The component agarose consists of units of agarobiose and agaropectin, which is carrying D-galactose and L-galactose unit, respectively. This component is mainly obtained from algae having a jelly-like texture. Agar is generally used as an alternative for gelatin, as a thickener, and a clarifying agent. Moreover, agar can be well explored to be used as a hydrogel in combination with active materials and other biopolymers, which has a great impact in the field of food packaging industry [8, 26]. The increasing urge for fresh food products with improved shelf life has inspired the researchers to derive new techniques to develop food packaging material. In this regard, hydrogel made up of agar with reinforced silver nanoparticle has a proficiency in extending the shelf life of fior di latte cheese, where fior di latte is a kind of fresh and semi-soft cheese which is generally produced in the style of Italian mozzarella, having elastic texture and pale yellow color and the silver nanoparticles performed as the active agent under in vitro condition [8]. The food products should keep proper color, odor, consistency, sensory, and all properties during the storage period. Further, silver nanoparticels are a remarkable candidate for formulation of active packaging, having limiting dose of silver ions of 0.05 mg of Ag/kg in food products [8].

2.4 Chitosan-Based Hydrogels

Chitosan is recognized as the widely available polysaccharide unit having property of biodegradability, biocompatibility, and nontoxicity and can be well utilized for developing hydrogels [50–52]. In addition, film formation is extensively acceptable by consumers because of antimicrobial, antihypertensive, antibacterial property of chitosan. This biopolymer can be extracted by deacetylation of chitin, and is available from crabs, shells, etc. [53]. The extracted chitosan can be well tailored in various forms to be utilized in various spheres of human life. Chitosan with immense properties provide an option to alter the use of fossil-based materials, which in turn reduces polymer-based waste.

The unmodified form of chitosan provides wide application, but presence of a number of functional groups in chitosan such as primary amine, primary and secondary hydroxyl group make a breakthrough for tailoring its property according to the need of forming ionic, covalent, complex cross-linking, multiple component-based networks (hybrid cross-links), composite-based networks (blends self-assembling networks) [54]. Chitosan is sensitive towards pH, temperature, ionic, electro responses, which impart a great impact on its usage. Further, chitosan-based hydrogels can be developed through reversible gel formations such as polyelectrolyte complexes, interpolymer matrix, hydrophobic associations, etc. In this way, chitosan is a perfect material for preparing better water-containing materials through various cross-linking networks. Chitosan can be mixed with other polymers with improved polymer-polymer interaction than water-polymer interactions to be used in food packaging and industrial applications. Further, in tissue engineering, chitosan-based hydrogels due to their biocompatibility material provide a wide array for use in the preparation of bone and scaffolds materials. Various design parameters may affect the property of physical and chemical hydrogel and formulation of chitosan with other materials that help in improving its properties in terms of better mechanical properties, biodegradability, biocompatibility, nontoxicity, plasticizing effect, etc. However, chitosan-based hydrogel in the field of food packaging applications are still underutilized, but they promise a wide potential for developing hydrogels in specified field.

2.5 Protein-Based Hydrogels

Proteins are being classified as one of the group of macromolecules generally consisting of long chains of amino acids linked together through peptide bonds [55]. Protein contains mainly amino and carboxyl groups; however, they also contain sulfur and phenyl group [55]. Proteins can be classified according to the molecule present in it such as simple protein consisting of amino acids only, conjugated protein consisting of non-peptide compounds and derived protein which is formulated through the action of heat, chemical actions, and enzymes. The examples of protein include elastin, collagen, hemoglobin, etc. [56]. Biopolymers of protein can be developed through condensation reaction, metal catalysis, enzyme action,

optimized environmental conditions, etc. In the past few decades, the utilized protein sources for producing biopolymers include casein, whey protein, whey protein isolates, soy protein, gluten, gliadin, pea protein, egg protein, etc. Besides this, various other kinds of vegetable and animal proteins are extensively utilized for the development of biopolymers. The development of hydrogel primarily depends on its structure, hydrophobic nature, types of bond involved, etc. Further, polysaccharide-based hydrogels with plasticizers are used for protein release. Considerably, protein biopolymers with unique properties can be cross-linked with other natural resources to be utilized in the field of food packaging application. Development of polyion-complex hydrogel films from gelatin and pectin component provide tailored properties with better mechanical and water resistance properties [24].

Combinations of biopolymers for forming hydrogels can be classified according to the selected polymers, bonds formations, methods of synthesis, as represented in Fig. 1. Cellulose-based hydrogels can be considered as a homopolymer, if only one kind of cellulose units has been taken for hydrogel development. Accordingly, they can be named as co-polymers, when the involvement of different polymer groups exists. Further, the formation of bond between molecules varies and can be reversible and irreversible depending upon the interaction type. If the cellulose molecules with selected molecules are linked through forming covalent bonds (chemical hydrogels), the resultant hydrogel will be irreversible and less prone to water absorption in various environment conditions. Synthesis of cellulose-based hydrogels through chemical hydrogel is preferable to store food products, where less water should penetrate through the packaging materials and can get a stable swelling stage depending on the interactions. In adverse, physical hydrogels are considered as reversible and unstable, which is less preferable to cellulose-based hydrogels due to weak bonding between polymer molecules such as hydrogen bonding, electrostatic interactions, ionic interactions, hydrophobic interactions, etc. Further, this type of hydrogel provides less resistance towards changing environment, which will be a harmful factor towards storage of food products within this hydrogel. Additionally, the factors such as nature of side groups of other polymeric materials, chemical, mechanical, and physical response towards relative humidity and temperatures should be considered before preparing cellulose-based hydrogel for the purpose of food packaging. Perishable food products are very prone to environmental conditions such as temperature, gaseous conditions inside the package which in turn depends on the oxygen transfer rate and water vapor transfer rate of the packaging materials, water uptake capacity, etc.

Further, the food products according to their shelf life can be classified as (1) perishable food products; (2) semi-perishable food products, and (3) shelf-stable food products. Among these, perishable food products have very less shelf life (3–4 days) and get spoiled easily in unfavorable environmental conditions. Example of perishable food products include milk and milk products, meat and meat products, fish products, poultry products, which should be kept in favorable environmental conditions for improved shelf life. The semi-perishable food has better shelf life than perishable food products and get spoiled only if handled carelessly and do not require refrigeration. This category of food products includes potatoes, onions,

salamis, pastries, etc. On the other hand, shelf-stable food products get spoiled over a long storage time and required no such storage conditions to improve shelf life, as this kind of products are generally pretreated earlier in such a way that possess longer shelf life such as rice flour, wheat flour, canned foods (dipped in sugar or salt solution), dried food products (dry fruits, nuts, pasta, etc.) etc. As mentioned, these products are prepared through the application of various unit operations such as drying, canning, etc. In concern with these categories of food products, cellulose-based hydrogels for food packaging application can be prepared with tailored properties according to the need. Moreover, chemical modifications of cellulose could provide a better way to improve the packaging property through grafting, cross-linking, blending, curing of molecules within the cellulose and other selected biopolymer molecules. Further, grafting can be initiated through initiator such as dicumyl peroxide, irradiation techniques, ionic grafting, etc.

3 Properties of Cellulose-Based Hydrogel for Food Packaging Application

The properties of hydrogels for food packaging application mainly depend on the formation of electrostatic interactions, covalent bonds through cross-linkers, network formation through interpenetrating polymer networks. Chemical composition of nonionic-based hydrogels is a principle factor to be considered for determining swelling. The parameters of hydrogels can be well-studied through various techniques such as film thickness, hygroscopicity, color, and transparency. The swelling properties of ionic-based hydrogels are mainly dependent on the pH of the components. Some of the considerable properties of hydrogel films are detailed below which include swelling mechanism, chemical properties, wettability, barrier properties, etc.

3.1 Swelling Property

The swelling property of dry hydrogels lies within its hygroscopic nature, which provides limitation to its use as food packaging materials. Swelling of matrix will start after the dried hydrogel starts to captivate water molecules from environment. As a result, the process of combining water to the polar ends begins and swelling of the dried hydrogels starts, which is considered to be a disadvantage of using hydrogel as food packaging materials. Physical state of water differs within the hydrogel due to swelling, which can be well studied by differential scanning calorimetry [57]. In polysaccharide-based hydrogels, the molecules of water categorized on the basis of non-freezing, freezing, free, and bound water and phase transition phenomena. Glass transition state of water, crystallization, and melting property of water present in hydrogel directly effects the water physical state within the hydrogel [33]. Additionally, due to the driving forces between hydrogel networks, the layers will absorb more water towards many dilutions, where the

absorbed water within this region fills all the large pores spaces, network spaces, and middle of macropores. Thus, the absorbed water may degrade the hydrogel films by disintegrating it into various pieces, where the degree of disintegration truly depends on the chemical property and composition of the films. The covalent bond due to chemical interactions can be a barrier to this process of swelling water within the pores and centers and networks. As a solution to this problem, combination of biopolymers can be utilized to develop hydrogels for proper food packaging materials with tailored properties, where polymer-polymer interactions could be the dominating factors over water-polymers interactions. The principle reason behind this improved polymer-polymer interaction between the molecules is the various structures and chemical composition molecules, which can link with themselves by forming bonds (such as covalent bonding), resulting in neglecting water and polymer interactions within the molecules. The amount of moisture retained (W_r) and equilibrium swelling ratio (eq_{sw}) can be calculated using stated Eqs. 1 and 2 [58, 59].

$$W_r = \frac{W_s - W_d}{W_s} \times 100 \tag{1}$$

$$eq_{sw} = \frac{W_s}{W_d} \tag{2}$$

where W_s and W_d represent weight of swollen hydrogel and dry hydrogels, respectively.

3.2 Chemical Properties

The chemical properties of the selected biopolymers are very crucial to be considered for having a remarkable role in the field of biodegradable hydrogel for acting as a food packaging material. Depending on the chemical properties, the selected polymers will link through chemical- and physical-based hydrogel. Further, if more than one biopolymer is present than more polymer-polymer interactions will be dominating one over polymer-water interactions. The study of chemical compositions can be well studied by Fourier transform infrared spectroscopy, attenuated total reflectance in case of films [34, 60, 61], and NMR study can provide in depth study on interactions of polymer in hydrogel [62]. Further, by studying the functional group available in the individual and mixed polymer compositions, grafting mechanism and cross-linking mechanism along with information about the formed functional groups will be known. Polymer grafting is a mechanism of linking two polymers, where the functional group of one polymer will attach to the backbone of other polymer forming a new functional group, which will change the functionality of the formed groups. As discussed, grafting can be of various kinds as follows (1) free radical grafting, where an initiator will start reaction by generating free radical molecules; (2) grafting through living polymerization, where living polymers themselves have the ability to react for a long time ignoring the degree of reaction termination is negligible; (3) ionic grafting which

proposed ionic line (Cationic and anionic mechanism) for grafting; (4) grafting by irradiation technique, where polymer irradiation approach are followed to generate free radicals, and (5) photochemical grafting, where grafting of polymer molecules occur due to the presence of chromophore in polymer molecules, which absorbs energy and shifted to higher energy orbital and others.

3.3 Wettability

The wettability of the hydrogel films can be measured by using contact angle analyzer, where the microdrops of liquid are poured onto the films. The resultant contact angle is captured by a digital camera which further determines the surface property and energy. The wettability of materials mainly depends on the hydrophilic and hydrophobic property of the materials, which in turn depends on the surface attraction of the films towards selected liquids determining surface tension. The higher attraction of specimen towards the selected liquid defines the hydrophilicity of the specimen, where the specimen is noted as hydrophilic material possessing low contact angle. On the other hand, hydrophobic material possesses no attraction towards liquids and have very high contact angle. The contact angle or wettability of selected specimens is measured using the Eq. 3, where ɵ represents the contact angle of the polymeric material.

$$\gamma_{sv} = \gamma_{sl} + \gamma_{lv} \cos\theta \tag{3}$$

where γ_{sv}, γ_{sl}, and γ_{lv} are the surface tension of solid vapor, solid-liquid, and liquid-vapor interfaces, respectively.

3.4 Color Determinations

High consumerization of any packaging material mainly depends on the customer acceptance and the customer will firstly observe the color of packages, whether the stored food items are visible or not from outside. So in this sense, the color of food packaging materials plays a critical role in the field of global marketing of the polymers. The advantage of transparent packaging materials is easily convenient to the customer for observing the conditions of food products whether it is safe or on the verge of spoilage. For this reason, the color parameters (L*, a* and b*) and color kinetics of packaging material are studied to know about the effect of environmental conditions such as temperature, gaseous conditions, on packaging materials. The color parameters are generally measured by Hunter color lab, portable colorimeter, spectrophotometer, and others. Each color parameter has some significance over other parameter. In addition to L, a*, b* values, other parameters such as hue, chroma have some specified norms in the color measurement phenomena [63]. Theoretically, the factor L* describes about the variation of darkness (L* = 0 indicates perfect black) to lightness (L* = 100 indicates perfect white); a* specifies degree of redness (+a) and greenness (−a); and b specifies the degree of yellowness (+b) to

blueness (−b). From L, a*, b* value hue angle (H°), chroma (C*) and total color differences (ΔE) can be determined using the detailed Eqs. 4, 5, and 6, where hue angle specifies the most dominating color and chroma specifies about the saturation of coloring material present. Further, hue angle of 0°, 90°, 120°, and 240° specifies the coloring effects of red, yellow, green, and blue, respectively. So in this regard, color determination of hydrogels provides the information regarding the consumerization of hydrogels as packaging material.

$$\text{Hue angle} = \tan^{-1}(\text{b}/\text{a}) \tag{4}$$

$$\text{Chroma} = \sqrt{\left(\text{a}^2 + \text{b}^2\right)} \tag{5}$$

$$\Delta E = \sqrt{(\Delta L)^2 + (\Delta a*)^2 + (\Delta b)2} \tag{6}$$

3.5 Water Vapor Uptake Ratio, Water Vapor Adsorption Kinetics and Water Vapor Adsorption Isotherm

The water barrier properties of hydrogel can be understood by understanding the water vapor permeability (WVP), water vapor uptake ratio, water vapor adsorption kinetics, and water vapor adsorption kinetics [26].The barrier properties of hydrogel films play a crucial role for acting as a food packaging material. The water vapor transmission rate can be measured using gravimetric method following ASTM E-96-95 [26]. According to reported study, WVP can be determined under 50% RH at 25 °C using following Eq. 7.

$$\text{WVP} = \frac{\text{WVTR} \times \text{y}}{\Delta \text{p}} \tag{7}$$

where y, Δp, and WVTR represent the mean film thickness, partial water vapor pressure difference through two sides of the hydrogel films, and water vapor transmission rate.

The water vapor uptake ratio (WVUR) is another critical parameter to be considered for proper storage of food products as they are greatly influenced by the presence of water vapor, which can be determined by using Eq. 8. Further, the presence of inadequate amount of water vapor may create detrimental effect to the food products. The water vapor absorption study can be efficiently carried out by using saturated solution of KNO_3 under constant temperature of 25 °C for 24 h.

$$\text{WVUR} = \frac{\text{W}_\text{a} - \text{W}_\text{b}}{\text{W}_\text{b}} \times 100 \tag{8}$$

where W_a, W_b denote weight of hydrogel films after and before dipping, respectively.

Moreover, a method for determining water vapor adsorption of hydrogel films include dispersion of specific amount of hydrogel film in saturated KNO_3 solution.

KNO_3 solution should be kept in Fido airtight glass jar having a silicon gasket and clamp lid, which is generally utilized to obtain constant relative humidity. In this study, water vapor absorption kinetics can be studied by a plot between weight increment against storage time, where equilibrium water content and rate constant of water vapor adsorption are acquired.

In the year 2013, Rhim has followed static gravimetric process to obtain water vapor adsorption isotherms of hydrogel-based films [26]. In the study, hydrogel-based film samples are kept at different saturated salt solutions at static water activity, and equilibrium moisture content was taken after 20 days. Further, use of GAB model (Eq. 9) is sufficient to fit the data of hydrogel film samples. Moreover, parameters of GAB model can be well obtained by Marquardt-Levenberg algorithm utilizing Solver function of Excel®.

$$W = \frac{W_O C k\, a_w}{(1 - k a_w)\ (1 - k a_w + C k a_w)} \tag{9}$$

where k is a parameter equivalent properties of multilayer molecules in regards with bulk liquid, C is the Guggenheim constant, a_w water activity, w, w_0 denote the equilibrium moisture content at a_w in dry weight basis and moisture content of mono-molecular layer on the internal surface of hydrogel films.

3.6 Mechanical Properties

The mechanical properties of the food packaging material are important parameter to be considered for having a great application in the field of packaging materials. The mechanical properties of films mainly depend on the cross-linking and intermolecular bonds between polymer molecules which mainly include tensile strength, elongation at break, elasticity of modulus, and can be measured following the ASTM standard D882–88 using Universal Testing Machine.

3.7 Antibacterial and Antimicrobial Activity

Antimicrobial and antibacterial activity of hydrogel relates to the presence of active compounds in hydrogels, which cause no harmful effect to the food constituents present inside the package. Further, both the activities can be tested against microbes.

3.8 Packaging Test

The usefulness of packaging materials is determined by storing an amount of perishable food products inside packaging materials. The storage of food products should be done at predetermined storage conditions, which will enhance the product

quality. Low temperature and low gas concentrations are preferable for long-term storage of fruits and vegetable products. With increase in temperature, the molecular randomness increases which results in increasing respiration rate of food products. Moreover, anti-fogging effect of packaging materials is another factor concerned with improved shelf life of food products.

4 Application of Cellulose–Based Hydrogel in the Field of Food Packaging

Polyvinylpyrrolidone (PVP) and carboxymethyl cellulose (CMC)-based hydrogel for food packaging PVP is a synthetic, water soluble polymer unit consisting of N-vinylpyrrolidone (Fig. 4) having a wide application in the field of medical, food packaging, food industry as emulsifiers, thickeners, food stabilizer, and as membrane material, which is further used in making daily used products such as toothpastes, hair gels, hair sprays, shampoos, etc. [64–68]. Remarkably, in food engineering and technology, PVP is greatly used for preserving food flavors, retains food quality, and acts as refining agent in beer and wine industry and others [63, 69, 70]. Further, the hydrophilic nature of PVP is discovered in the year of 1939, so having water solubility and providing an ability towards film forming property can be used for making dry and wet films with tunable mechanical properties.

CMC is a cellulose derivative which is biodegradable, hydrophilic, and is used in wide variety of application including food packaging, biomedical, textile industry, and others. CMC is a kind of ether derivative of cellulose, where H atoms of hydroxyl groups of cellulose are substituted by carboxymethyl unit [71]. It is predicted that the world market of using CMC may spread up to 892 million pounds by 2017. The utilization of CMC in the field of food packaging with other available biopolymers such as gelatin, chitosan, lipids, glycerol, starch are widely observed for making edible food packaging in the form of films and coatings [72–75]. In addition, the mixing of other biopolymers with CMC aims to improve the properties in terms of improving its physical property such as mechanical properties, thermal stability, barrier properties (oxygen transmission rate and water vapor transmission rate), which helps in improving shelf life of perishable food products. Considerably, for improving barrier properties of films, both solubility and diffusivity should be

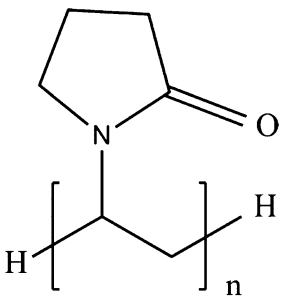

Fig. 4 Chemical structure of PVP

improved with the effect of added material to reduce permeability of oxygen and water vapor.

The combined use of PVP and CMC in developing hydrogel has an important role in the field of food and beverage industry. In this regard, PVP-CMC-based hydrogel films has many significant properties essential for packaging application including flexibility, transparency, water-retaining capability, and breathable film, which retain freshness of the food products for long duration. Combined effect of different factors such as temperature range, relative humidity, and storage period may significantly affect the properties of PVP-CMC-based hydrogel, which are considered crucial factors for food packaging. A study on developing PVP-CMC-based hydrogels using solution casting method were reported, where individual polymer solutions were prepared in the controlled environment of moist heat exploration [34]. The development of PVP-CMC-based hydrogel is carried by following steps: (1) Preparation of individual polymer solution, (2) treatment of the polymer solution at 120 °C under 15 lbs. pressure for a period of 20 min, and (3) finally, solution casting method is followed to obtain the targeted PVP-CMC-based hydrogel. Interestingly, agar, glycerine, and poly ethylene glycol were added to the mixture for formulating the hydrogel, which provide PVP-CMC-hydrogel with a thickness of 0.09–0.1 mm. The functional groups in the hydrogel can be detected using FTIR spectroscopy in line with attenuated total reflectance (wavelength range: 4000–400 cm^{-1}). Further, for acting as a food packaging materials, combination of materials should improve the mechanical properties, under dry atmosphere, where the PVP-CMC-based hydrogel attain 45.6 ± 1.5, 45.5 ± 1.9, and 42.2 ± 4.3 MPa of tensile strength at 25 °C, 35 °C, and 45 °C, respectively, in comparison to CMC which has 43.7 ± 3.3, 42.1 ± 7.3, 45.7 ± 3.9 MPa of tensile strength at 25 °C, 35 °C, and 45 °C, respectively. So the combination of materials has been found to improve the mechanical properties. Further, E-modulus also improved in comparison to CMC when PVP were mixed to prepare the hydrogel. The E-modulus of PVP-CMC was 2183 ± 183, 2213 ± 83, 1957 ± 55 MPa at 25 °C, 35 °C, and 45 °C, respectively. On the other hand, CMC has 1722 ± 158, 1816 ± 287, and 1977 ± 380 MPa of E-modulus at 25 °C, 35 °C, and 45 °C, respectively. The development of PVP-CMC-based hydrogel has been explored for stringent food packaging, providing better mechanical and hydrothermal effects in comparison to neat CMC hydrogels. The addition of PVP in CMC provide an inhibitory action to the plasticizing effect of moisture till 50% RH, and this combination of hydrogel provide higher stability under hydrothermal treatment. The swelling and de-swelling effect of PVP, CMC, PVP-CMC hydrogel-based films provide a clear image about the cross-linking, ionic strength, physical cross-linking within the polymer molecules. At pH 6.5, the water absorption capability of CMC and PVP-CMC remain similar, whereas PVP shows a different kind of behavior by absorbing less amount of water in comparison to CMC and PVP-CMC. The water absorbing capability of the hydrogels remains maximum in the first 15 min, which is 12.05 ± 0.33 g/g, 4.20 ± 0.16, and 10.82 ± 0.50 g/g for CMC, PVP, and PVP-CMC hydrogels, respectively. Further, with increase in time the water absorption capacity uniformly increased and reached an equilibrium state. Both CMC and PVP-CMC

hydrogel films provide good water holding ability upto 120 min. The water holding capability of PVP, CMC, and PVP-CMC at around 30 min are 76.47 ± 0.97, 84.99 ± 0.38, and 83.84 ± 1.0%, respectively. The storage modulus of PVP-CMC hydrogels is found to improve in comparison to CMC hydrogel. In adverse, with increase in %RH, the storage modulus decreases for both the hydrogels, i.e., CMC and CMC-PVP. The storage modulus of CMC is 2940, 2580, 1060, 90, 40 MPa at %RH of 0, 10, 30, 50, and 70, respectively. For PVP-CMC, the storage modulus is 3260, 2990, 2020, 180, 70 MPa at 0, 10, 30, 50, and 70%RH, respectively. It is reported that, the PVP-CMC hydrogel provide lower creep compliance than CMC during creep and higher strain recovery. Further, formation of physical cross-linking between PVP-CMC hydrogel can be obtained with increase in temperature and the differentiation between the surface morphology, structure, and topography, internal structure of hydrogels can be well studied by using SEM and AFM. So in conclusion, blending of biopolymers with synthetic polymers with enhanced polymer-polymer interactions than water-polymer interaction could provide better materials for food packaging. The tailored properties of food packaging materials as hydrogels can be obtained through irreversible bond formations through covalent chemical bonding, intramolecular and intermolecular bonds, physical bonding through distinct polymer networks.

5 Biodegradability of Cellulose–Based Hydrogels for Food Packaging Application

Biodegradability of bio-based hydrogels provides an ideal breakthrough for the design and progress of stringent food packaging material, where they possibly make an effort towards the environment friendly packaging material [76, 77]. Involvement of microorganism to the biodegradation process of films is considered as a primary degradation approach. Under controlled atmosphere, the biodegradability of biopolymer-based hydrogels are promising, where change in the property of films with storage period provide the mechanism of degradability. Considerably, the most prominent parameters affecting the biodegradation process of films are chemical functional property, wettability (hydrophobic or hydrophilic), swelling and de-swelling nature, molecular weight, morphology, etc. [34]. In addition, deviation of films under observation for biodegradability can be well studied by observing the functional group degradation, wettability, surface morphology, mechanical properties, molecular weight, thermal stability, etc. Evaluation of CO_2 is another significant factor for observing the degradation process. In this regard, biodegradability, biocompatibility, and nontoxicity nature of cellulose-based hydrogel is an essential property that needs to be considered for using as a food packaging material. In addition to biodegradability of packaging material, the hydrogels should provide protective and preservative action to the food substances. Biodegradation study of hydrogels can be done using Czapek-Dox liquid medium having constituents of glucose, dipotassium phosphate, magnesium sulfate, sodium nitrate, ferrous sulfate, and soil extract, which are used as inoculums for composting and the biodegradation

of CMC, PVP, agar, glycerin, and PEG can be easily done by aqueous solution [34]. The stability of chemical properties of hydrogels within the period of biodegradation study can be studied through using FTIR. The immense alternation of chemical composition makes changes in the nature of peaks, which defines the molecular interactions within the biopolymers. Further, the inoculated microorganism in liquid medium increases with time, which will put a positive impact to the biodegradation method by metabolizing products. The surface morphology provides an evidence supporting the biodegradation study through deposition of microorganism or insoluble products produced by microorganisms. PVP-CMC-based hydrogel provides durable storage modulus defining elastic properties within 2 weeks of biodegradation, which directs about carrying elastic properties of the hydrogel within 2 weeks of storage [34]. Noticeably, storage modulus of PVP-CMC hydrogel decreases after 6 weeks of biodegradation study, and after 6 weeks of storage, the elastic property decreases prominently tending towards extending viscosity. PVP-CMC hydrogels provides better elastic property than viscous property. Weight loss is a considerable parameter for defining the biodegradation study of hydrogels. The % weight loss of PVP-CMC hydrogel obtains up to 10% and 38% for 2 and 8 weeks, respectively. The change in mechanical properties of dry hydrogel of PVP: CMC in the ratio of 20:80 in terms of E modulus during the period of biodegradation are ~ 1423.33, 1322.77, 1303.76, 1394.41, 1502.37 MPa for 0, 1, 3,5,7 weeks, respectively [34]. In addition, the tensile strength of specified hydrogel is ~20.93, 26.56, 25.56, 26.67, 30.62 MPa for 0, 1, 3, 5,7 weeks, respectively. In this regards, the hydrogel based on PVP, CMC, PEG, glycerin, and agar are considered as nontoxic and biodegradable films providing immense property to provide fresh fruits and vegetables an apposite storage for improved shelf life [34]. Similar to the PVP-, CMC-, PEG-, glycerin-, and agar-based hydrogel, other cellulose-based hydrogels can be formulated based on biopolymers cellulose derivatives, gelatin, starch, chitosan, protein isolates, pectin, and synthetic polymers poly (vinyl alcohol) with improved properties for acting as biodegradable hydrogel for food packaging applications.

6 Conclusion

Cellulose is extracted from bio-based renewable resources, which is widely available in nature. Cellulose-based hydrogels are biocompatible, eco-friendly, nontoxic material having immense capability to keep food products fresh and lively. This chapter highlighted the recently formulated cellulose-based hydrogels as a substitute to food packaging material. Moreover, combination of other polymer materials to the cellulose is found to impart tailoring properties to the hydrogel for acting as a food packaging material. The cellulose-based hydrogel have the ability to store fresh fruits and vegetables which release moisture as hydrogel has the ability to trap moisture. So considering this, an enormous research must be carried out to develop hydrogels based on the cellulose and its derivative for providing an alternative to the food packaging application.

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Moisture Sorption Isotherm and Isosteric Heat of Sorption Characteristics of PVP-CMC Hydrogel Film: A Useful Food Packaging Material

35

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Contents

Abstract

Hydrogels are polymeric materials possessing a three-dimensional network structure and can absorb a large quantity of liquid water. Recently, hydrogel-based polymeric materials are being focused and encouraged as they are breathable and maintain the shelf life of fresh fruit and vegetables. A hydrogel film was prepared using synthetic polymer, polyvinylpyrrolidone (PVP), and biopolymer, carboxymethyl cellulose (CMC) and agar, along with polyethylene glycol and glycerol as plasticizer to create a breathable and biodegradable film termed

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as "PVP-CMC" hydrogel film. In general, hydrogel film provides poor but composition- and structure-dependent moisture resistance in normal atmosphere. Further, interaction among the plasticized ingredients, which are dependent on its ultimate moisture content, controls the physical and mechanical properties of the film. Therefore, it is important to know moisture sorption characteristics of each hydrogel film. The "PVP-CMC" hydrogel film exhibited a tendency to adsorb/desorb moisture depending on environmental relative humidity and temperature during storage. Hence, the general features and the equilibrium relationship between moisture contents of "PVP-CMC" hydrogel film at different temperatures (25, 35, 45 and 55 °C) and relative humidities (≈ 10–90%) of the environment in which the film generally resides, i.e., moisture sorption isotherm (MSI), will be discussed in this chapter. The isosteric heat of sorption at different moisture contents of "PVP-CMC" hydrogel film will also be discussed.

Keywords
PVP-CMC hydrogel film · Moisture sorption isotherm · Isosteric heat · Water activity · Moisture content etc

1 Introduction

Hydrogels are hydrophilic three-dimensional networks of polymer chains capable of imbibing, without dissolution, large amounts of liquid water, in the order of hundreds to thousands of times of their dry weight. Owing to this high soaking and retaining capacity, hydrogels have long been applied as absorbent in health care system (e.g. diapers, sanitary napkins, etc.), industrial system (e.g., municipal water treatment, muddling, etc.), as well as horticulture and agriculture (soil additive, germination of seedlings, etc.) [1]. It has also been used as controlled release systems of drugs, a carrier of water and pesticides in agriculture field [2], and help in increasing the water holding capacity of soil, because addition of hydrogel in soil could decrease the irrigation requirement of many plants and hence could be especially useful in rain-fed agriculture or farming [3, 4]. The mechanism of water intake in the hydrogel matrix is clearly mentioned by Farrisa et al. [5]. According to them, when a dry hydrogel begins to absorb water, hydration occurs at the most polar hydrophilic groups leading to swelling of the matrix. As the matrix swells, the network exposes hydrophobic groups that have a natural tendency to resist water molecules. Along with these concomitant interactions, the hydrogel intakes additional water due to osmotic driving force within the network chains, resulting in infinite dilution. The additional swelling water is supposed to fill the space between the network chains, macropores, and voids.

Several petroleum-based synthetic polymers (e.g., low-density polyethylene (LDPE), polyethylene terephthalate (PE), high-density polyethylene (HDPE), polyvinylidene chloride (PVDC)) are being employed for preparation of food packaging [6]. However, considering non-biodegradability of these synthetic polymers, scientists are now concentrating toward development of biodegradable food packaging

as alternatives. In this line of research, Roy et al. [7, 8] fabricated cellulose-based hydrogel food packaging material which is breathable and biodegradable This cellulose-based hydrogel food packaging was prepared by mixing several ingredients including three biopolymers: polyvinylpyrrolidone (PVP, synthetic water-soluble biodegradable polymer), carboxymethyl cellulose (CMC, natural/renewable and superabsorbent biopolymer), and agar (natural/renewable and structural biopolymer) [7, 8]. CMC is abundantly available among all the natural polysaccharides.

Due to lightweight, transparency, heat sealability, resistance to water, and low cost, petroleum-based synthetic polymers [6] are widely used flexible packaging material for fresh fruit and vegetables. Despite these advantages, environmentalists are now emphasizing replacement with materials from biodegradable resources, i.e., poly(hydroxybutyrate) (PHB), polylactic acid (PLA), polyhydroxyapatite (PHA), etc. [9, 10], because such petroleum-based polymer films are neither totally recyclable nor biodegradable. For multilayer films, recycling is not possible at all. Respiration and transpiration processes of fresh fruit and vegetables still continue after harvesting. And therefore, if these food stuffs are packed in packaging prepared with petroleum-based polymer film, there is frequent accumulation of water vapor inside the package because the synthetic petroleum-based polymer film is moisture impermeable [11]. Such accumulation enhances the relative humidity (RH) of the enclosure, ultimately deteriorating the content's color and texture and gradually initiating spoilage to affect the nutritional and microbial quality. Mahajan et al. [12] conceptualized that biopolymer-based film that can absorb and permeate water vapor may be appropriate for packaging respiring items. Saha et al. [13] also noticed that the biopolymer-based hydrogel food package is more breathable compared to traditional food packages, and the test sample, table grapes, remained as good as fresh until 3 weeks. No ethanol formation/fermentation process is initiated during the 3-week storage time. Very recently, Sen [14] observed that starch film with water vapor absorbing capacity could extend the shelf life of strawberry, banana, and apple over synthetic film, as hydrogels are highly water absorbing, Farris et al. [5] professed that hydrogels could also offer new opportunities for design of efficient biopolymer packaging materials. Roy et al. [7, 8] first opined that in water-soluble polymer solution made through moist heat treatment when cast into films and dried, the fabricated film possessing the properties of pseudo-hydrogel [5] could be used as a packaging material for fresh fruit and vegetables.

When a commodity packaged in dry hydrogel film would be subjected to storage, the ingredients in the film, due to their hydrophilic character (of course controlled by composition), would absorb/desorb moisture in vapor phase depending on environmental RH and temperature – the process will continue till the moisture content of film reaches the equilibrium value, i.e., equilibrium moisture content (EMC). This will change the film's water activity (a_w), a measure of the energy status of the moisture content in a system, which was originally present in dry condition. Finally, the achieved a_w at EMC equals the RH of that environment. For biopolymer-based materials, water activity controls several criteria including mechanical and permeability properties, heat sealability, and chemical and microbial instability [15]. Moisture sorption isotherm (MSI) provides the graphically expressed profile of the

amount of water molecules (EMC) that any substance will hold when exposed to air at a certain temperature with different relative humidities and, therefore, is an essential tool for the design of packaging and storage system of food. Hence, it is important to know the MSI characteristics of any film prior to its fruitful application.

Developing MSI empirically is time-consuming and costly as well. Modeling, i.e., representation of sorption data with the best-fit mathematical equation, helps to generate the MSI at an unknown temperature within the temperature range for which the MSIs have already been experimentally evaluated. MSI of biopolymer-based films prepared with various raw materials like cornstarch, tapioca starch, cellulose derivatives, whey protein, peanut protein, etc. has been modeled by several workers [14, 16, 17], but there is no reported information about the MSI of dry biopolymer film, e.g., "PVP-CMC" hydrogel film.

A thermodynamic parameter such as net isosteric heat of sorption (q_{st}, defined as the total heat of sorption of water on any material minus the heat of vaporization of water, at the system moisture content) is frequently computed from MSI data at different temperatures [14, 18]. It is an important parameter in assessing the water activity of packed food material with fluctuation of temperature to assess the shelf life, vis a vis efficiency of packaging film.

This chapter discusses briefly about preparation and general characteristics of biopolymer- and biodegradable polymer (cellulose)-based hydrogel film designated as "PVP-CMC" hydrogel film that performs as a prospective food packaging material. Further discussed are moisture sorption characteristics of this film in detail, i.e., moisture sorption isotherm (MSI), followed by estimation of net isosteric heat of sorption (q_{st}).

2 PVP-CMC Hydrogel Film

2.1 Preparation

The "polyvinylpyrrolidone-carboxymethyl cellulose" (PVP-CMC) hydrogel film was prepared by solution casting method. The film-forming polymeric solution was prepared by dissolution of a mixture comprising of polyvinylpyrrolidone (PVP, 0.2%), carboxymethyl cellulose (CMC, 0.8%), agar (2%), polyethylene glycol (PEG, 1%), glycerin (1%), and water 95% [7, 8, 13], where the % refers to weight/volume (w/v). For dissolution, all the polymer mixture taken in a sealed glass bottle was subjected to moist heat treatment, where pressure (107 kPa) and heat (120 °C) for 20 min were maintained. Thereafter, the hot polymer solution (≈ 150 ml) was poured into the well of the polyethylene-fabricated square plate (25 × 25 cm) as showed in Fig. 1. The gel mass was allowed to cool for 2–3 min for the formation of soft and solid biomaterial as a pseudo-hydrogel having super-absorbent potentiality. The soft mass of hydrogel was allowed to dry at room temperature (22–25 °C) for 24 h. Finally, transparent, thin, square-shaped, dry, and flexible film, designated as "PVP-CMC" hydrogel film [7, 8, 13], was obtained.

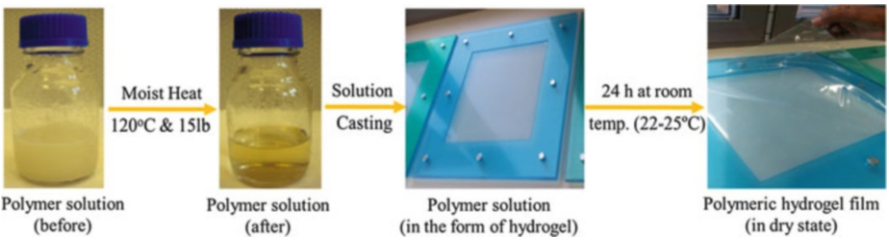

Fig. 1 Scheme showing the preparation of "PVP-CMC" hydrogel film

The scheme for the development/preparation of "PVP-CMC" hydrogel film is depicted in Fig. 1.

2.2 Properties

2.2.1 Physical

The "polyvinylpyrrolidone-carboxymethyl cellulose" (PVP-CMC) hydrogel film prepared with PVP/CMC = 20:80 is thin (0.1–0.2 mm), transparent, flexible, nontoxic, and self-supporting. A visual image of a food package with "table grapes" which was prepared with "PVP-CMC" hydrogel film is shown in Fig. 2. Being a hydrogel film, it has some advantageous properties as food packaging material, especially for the fresh fruits, vegetables, and the food stuff which release moisture, as reported by Saha et al. [13]. The "PVP-CMC" hydrogel film can simultaneously absorb and release moisture (generated from/by fresh fruits and vegetables) and keep the environment of the package arid and also maintains the diffusion of oxygen; as a result, it prevents the food materials from fast decay [7, 13]. Additionally, this hydrogel film revealed a remarkable biodegradability [8].

2.2.2 Mechanical, Viscoelastic, and Thermal

The mechanical properties of dry "PVP-CMC" hydrogel were investigated by dynamic mechanical analysis (DMA) (transient stress-strain analysis) in a dry atmosphere, i.e., at 0% relative humidity (RH). The acquired mechanical properties as a function of 25, 35, and 45 °C temperatures at the dry atmosphere are shown in Table 1. Tensile strength and strain at break of PVP/CMC = 20:80 hydrogel film sample is very similar to the neat CMC sample, the superabsorbent polymeric biomaterial [19]; after an increase in temperature from 25 °C to 35 °C, there were no significant changes in mechanical properties. Nevertheless, the increase of temperature to 45 °C influenced slightly on elastic modulus (E-modulus) [19].

Contrariwise, if the mechanical properties of the dry PVP/CMC = 20:80 hydrogel film were investigated on a tensile testing machine (Instron 8871) at 25 °C and 58% RH, different values of E-modulus and tensile strength, i.e., 1423.33 ± 106.61 MPa and 20.93 ± 1.24 MPa, respectively, were obtained [8]. The mechanical strength properties of such hydrogel film gradually decrease during

Fig. 2 The food package prepared with "PVP-CMC" hydrogel film

Table 1 Stress-strain analysis data of "PVP-CMC" film at dry atmosphere (average value ± SD, $n = 5$) [19]

	PVP-CMC hydrogel film		
Mechanical property	25 °C	35 °C	45 °C
Tensile strength at break (MPa)	45.6 ± 1.5	45.6 ± 1.9	42.2 ± 4.3
Tensile strain at break (%)	7.4 ± 1.7	6.7 ± 0.6	8.2 ± 2.8
E-modulus (MPa)	2183 ± 183	2213 ± 83	1957 ± 55

biodegradation phase; on the other hand the values of tensile strength properties gradually increase with biodegradation time/duration. For example, it can be described that after about 3 weeks of biodegradation sample of PVP/CMC = 20:80 hydrogel film shows 1303.76 ± 187.33 MPa and 25.56 ± 2.50 MPa, respectively, as E-modulus and tensile strength [8]. This happened may be due to the following reasons: The values of E-modulus are decreasing initially due to slow degradation of the polymer film in the liquid state and then increasing slowly due to the penetration of microbes/microbial growth within the film matrix. During degradation period, the said hydrogel film is transformed from flexible to brittle.

Here, it can be mentioned that not only measurement conditions or film conditions (whether biodegradable or not biodegradable) have influence on mechanical properties of "PVP-CMC" hydrogel film but the device used for evaluation of mechanical property also has a great role.

Viscoelasticity denotes the combination of viscous and elastic properties of a material with the relative contribution of each being dependent on time, temperature, stress, and strain rate [20]. Roy et al. published, in wet state (just after preparation, before dry), the PVP-CMC hydrogel itself revealed a strong elastic property and

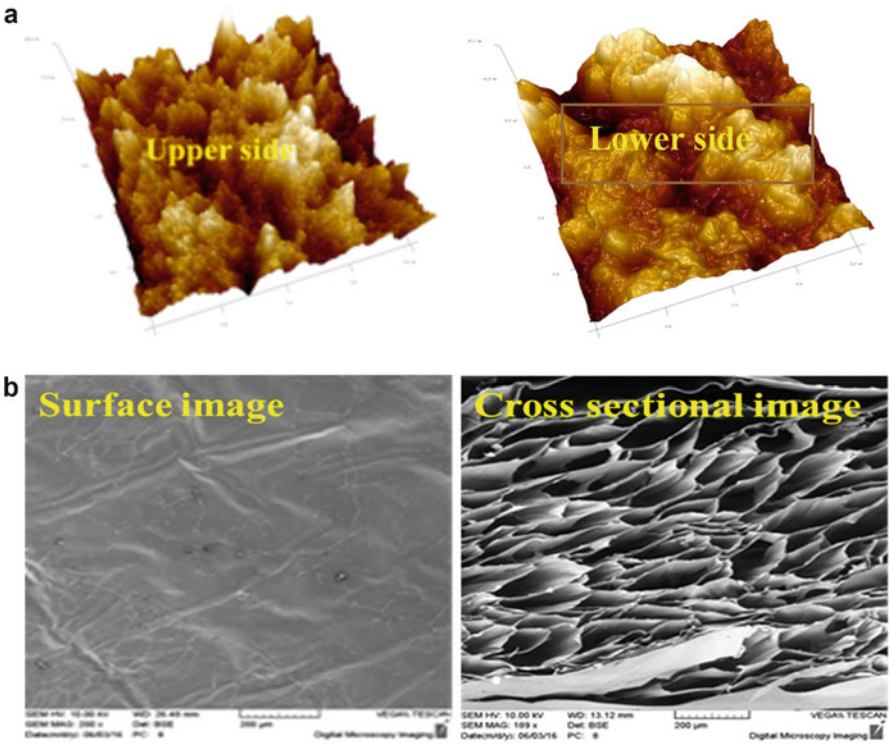

Fig. 3 (**a**) Structure of "PVP-CMC" hydrogel food package film (AFM). (**b**) Structure of "PVP-CMC" hydrogel food package film (SEM)

holds this strong elastic property until 2 weeks of biodegradation (biodegradation study performed in liquid state) [8].

Concerning thermal properties point of view, dry PVP-CMC hydrogel film is sealable. It is possible to prepare food package using a heat sealing apparatus at 50 °C. At high temperature (i.e., above 60–70 °C), dry PVP-CMC hydrogel film gets damaged.

2.2.3 Structural

Both scanning electron microscopic image (SEM) and atomic force microscope image (AFM) provide structural information about any material. The structure of "PVP-CMC" hydrogel film (used as a food package for fresh fruit and vegetables) is depicted in Fig. 3a and b, which confirms that the surface of "PVP-CMC" hydrogel film is not smooth but rough with lots of ups and downs, though visually it looks smooth. The cross-sectional image of "PVP-CMC" film (Fig. 3b) confirms a three-dimensional cross-linked polymeric network inside – the typical porous structure of dry hydrogel film. The porous structure "PVP-CMC" hydrogel is an evidence of its breathability.

3 Moisture Sorption Characteristics of PVP-CMC Hydrogel Film

3.1 Generation of Moisture Sorption Isotherm, Modeling, and Net Isosteric Heat of Sorption

MSIs were generated by isopiestic vapor transfer technique (gravimetric method) by exposing the films to constant relative humidity environment created by saturated solution of assigned chemicals [21].

3.1.1 Preparation of Different Relative Humidity Environments

Saturated solutions of NaOH, CH_3COOK, $MgCl_2$, K_2CO_3, $MgNO_3$, $NaNO_3$, NaCl, KCl, and K_2SO_4 were used in respective vacuum desiccator to maintain the environment RH in the range of 10–90% (i.e., film's water activity (a_w) at 0.1 to 0.9) at nine levels, and the whole set kept in incubator at four temperatures, viz., 25, 35, 45, and 55 °C (Table 2). The process of preparing saturated salt solution involved dissolving a salt in distilled water in stepwise addition with continuous stirring by a spatula until the salt remained in excess and deposited at the bottom of the container. Solution was then heated to dissolve the deposited salt, followed by addition of more till undissolved salt appeared again at the bottom of the container, which ensured saturation of the solution in heated condition. Finally, the hot saturated solution was naturally cooled to ambient temperature and poured in desiccator to a level just below its platform. Similar technique was followed for all chemicals.

3.1.2 Determination of Equilibrium Moisture Content

Determination of equilibrium moisture content (EMC) of film, measured mass of film (in five replications), was taken in previously weighed weighing bottle, placed without lid in desiccator containing a saturated solution (provided in section 3.1.1) to maintain a particular RH. Partial vacuum was created inside the desiccator to accelerate the adsorption or desorption process. The series of desiccators for various RH systems was then placed in a temperature-controlled incubator maintained at 25 °C.

Table 2 Relative humidity (RH) of the environment at different temperatures

	Relative humidity (%)[a]			
Chemicals	25 °C	35 °C	45 °C	55 °C
Sodium hydroxide, NaOH	08.7	6.5	05.0	03.9
Potassium acetate, CH_3COOK	23.7	21.5	19.7	18.2
Magnesium chloride, $MgCl_2$	32.7	32.0	31.1	30.0
Potassium carbonate, K_2CO_3	44.3	43.6	42.9	42.4
Magnesium nitrate, $Mg(NO_3)_2$	53.6	51.5	49.7	48.1
Sodium nitrate, $NaNO_3$	74.2	72.0	69.9	68.6
Sodium chloride, NaCl	75.2	74.8	74.5	71.0
Potassium chloride, KCl	85.5	82.2	79.1	76.4
Potassium sulfate, K_2SO_4	97.2	96.7	96.2	95.7

[a]Film's water activity equals RH divided by 100

Film strips were allowed to equilibrate till it attained constant weight. This involved a period of 18 days (determined from a preliminary experiment). Following equilibration, bottles were taken out and the weight was noted. Dry weight of the film was determined by oven-drying method at 105 ± 1 °C for 24 h. Equilibrium moisture content (EMC) of the film was calculated using Eq. (1):

$$M_e(\%db) = \frac{W_{Eq} - W_{Dry}}{W_{Dry}} \times 100 \quad (1)$$

where M_e is the EMC on dry basis (in percent), W_{Eq} is weight of film after attaining equilibrium, and W_{Dry} is weight of film after removing the moisture in the oven. Similar procedure was performed for 35, 45, and 55 °C.

3.1.3 Modeling of Sorption Data

The experimental data were fitted to four MSI models, such as Guggenheim-Anderson-de Boer (GAB), Brunauer-Emmett-Teller (BET), Peleg, and modified Oswin. The mathematical expression of the model is presented in Table 3.

In the models, a_w represents the water activity/relative humidity in decimal (RH/100); M_e is the EMC in % (db); M_0 is the monolayer moisture content in % (db); T is the temperature in °C; and C, K, A, B, n, and x are sorption isotherm constants specific to each equation. Nonlinear regression analysis was used to calculate the various constants. Although not well defined, the monolayer (M_0) is often stated to represent the moisture content at which water attached starts to behave as liquid-like phase and corresponds with the optimal moisture content required for stability of low moisture materials [22].

3.1.4 Net Isosteric Heat of Sorption

The net isosteric heat of sorption (q_{st}) was calculated using Clausius-Clapeyron equation as given in Eq. (4):

$$\ln(a_w) = -\frac{q_{st}}{RT} + Z \quad (2)$$

where R is the universal gas constant, z is the integration constant, and T is the absolute temperature.

Table 3 Models applied to the experimental data

Model	Equation
BET	$M_e = \frac{(M_o C a_w)}{(1-a_w)(1+(C-1)a_w)}$
GAB	$M_e = \frac{M_o C K a_w}{(1-K a_w)(1+(C-1)K a_W)}$
Peleg	$M_e = K_1 a_w^{n_1} + K_2 a_w^{n_2}$
Modified Oswin	$a_w = \frac{1}{\left[\left\{(A+BT)M_e^{-1}\right\}^x + 1\right]}$

At any specific moisture content and using the best-fit MSI curve, corresponding a_w values at four temperatures were determined. A regression line (ln a_w vs. 1/T) was drawn using these data [23], and q_{st} was estimated from the slope of the straight line. This procedure was repeated for several other moisture contents in the range of 25–50%. It is worth mentioning that depending on the positive or negative sign of the slope, sign of q_{st} will be either negative or positive. According to the reference [23], the sign of q_{st} is purely a mathematical result and has no bearing with its physical interpretation. Thus, in this study only absolute values of q_{st} were considered [17].

3.1.5 Statistical Analysis

The mean value of EMCs and corresponding standard deviation (SD) was evaluated. The mean values were used only for all statistical calculation, model fitting, interpretation, and analysis of results.

Analysis of Variance and Least Significant Difference: Analysis of variance (F-test) is one of the most powerful and commonly used statistical tools that allow for the subdivision of the total variability into several causal components. Of a completely randomized design, there are two components of variation: (a) due to treatment and (b) due to experimental error. The relative size of these two components provides the basis of determining whether the observed differences among treatments are real or not. In the present study, F-test was carried out on EMCs for variation of a_w using a completely randomized design with equal replications [24]. Significant F-test assumes that the observed difference among the treatment means is real and not due to chance.

The least significant differences (LSD) among the median values of response, i.e., treatment means, were estimated at 1% or 5% probability levels ($LSD_{0.01}$ and $LSD_{0.05}$) to ascertain any significant difference among the pair of treatments.

Model Fitting: The suitability of the models was assessed using coefficient of determination (R^2), mean relative percentage deviation modulus (MRE %) (Eq. 2), root-mean-square error (RMSE) (Eq. 3), and residual plot [25, 26].

$$\text{MRE}\ (\%) = \frac{100}{N}\sum_{i=1}^{N}\left|\frac{M_{ei} - M_{pi}}{M_{ei}}\right| \tag{3}$$

$$\text{RMSE} = \left[\frac{1}{N}\sum_{i=1}^{N}\left(M_{ei} - M_{pi}\right)^2\right]^{1/2} \tag{4}$$

In Eqs. (3) and (4), M_{ei} is the ith experimental EMC value, M_{pi} is the ith predicted EMC value, and N is the number of experimental data. The residual plot is a plot of the difference between "actual value and predicted value" ($M_{ei}-M_{pi}$) versus actual value/predicted value/run number [25].

While the values of R^2 close to 1 and that of RMSE close to 0 indicate a better fit, MRE below 10% appears to be indicative of a good fit for practical purposes [27]. Regarding residual plot, acceptance of a model is built on its randomness, i.e., the data points tend to fall in a horizontal band around zero and show no clear pattern.

3.2 Equilibrium Moisture Content, Best-Fit Model, and Net Isosteric Heat of Sorption

3.2.1 Equilibrium Moisture Content

The mean EMCs along with the values of SD and LSD for different water activities at 25, 35, 45, and 55 °C are given in Table 4. At each temperature, F-test is positive, i.e., the obtained EMCs are controlled by a_w (i.e., RH) only and not by chance.

3.2.2 Best-Fit Model

The respective constants involved for each model and the error terms are shown in Tables 5 and 6. It is observed that for GAB, BET, and modified Oswin models, residual plots indicated pattern behavior for all the temperatures, while the Peleg model followed a random nature. Except at 45 °C, R^2 for other temperatures using BET model is poor; for the rest of the models, R^2 is close to 1 at all temperatures. The values of RMSE were located within the range 2–11 for GAB, 12–27 for BET, and 18.99 for modified Oswin. For Peleg, the range was relatively narrow spanning within 2–8. Considering MRE (%), it is less than 10 in 25% and 50% of cases for GAB and Peleg model, respectively. BET and modified Oswin model indicated considerably higher values of MRE. Thus, Peleg model is a good fit to the sorption data, and the estimated fitting parameters were statistically acceptable. Therefore, Peleg was considered as the best model for the present study.

3.2.3 Effect of Temperature on Moisture Sorption Isotherm (MSI)

The predicted MSI using the best-fit Peleg model of "PVP-CMC" hydrogel films at four different temperatures (i.e., 25, 35, 45, and 55 °C) is depicted in Fig. 4.

Irrespective of temperature, all the moisture sorption isotherms are found to be sigmoid in shape (type II according to BET classification), showing initial slow increase in moisture content for a_w up to 0.75 and a rapid increment with further augmentation of a_w. It takes into account the existence of sorption in multilayers for the available surface – typical characteristics of complex or polymeric materials [28]. Erbas et al. also stated that it is attributed to physical adsorption of water molecules on microporous (as showed in Fig. 3b for SEM image of cross section) solid and leads to multilayer formation [29]. Therefore, adsorption of moisture on the film proceeds with multilayer sorption mechanism, and the trend remained invariant temperature. Interestingly, the amount of moisture absorbed by "PVP-CMC" hydrogel film is much higher compared to starch film, particularly at high RH region [14, 17].

As seen from Fig. 4 that for a_w up to about 0.6, EMC increases with increase of temperature from 25 °C to 35 °C, following which there is a decrease with further increase to 45 °C and then to 55 °C. Possibly, there is structural orientation with change in temperature – exposing polar water binding sites for heating from 25 °C to 35 °C and collapsing for onward heating. From a_w value of 0.6 to 0.8, EMC follows the order for: 25 °C $\approx$ 35 °C $>$ 45 °C $>$ 55 °C, the trend common for biomaterials [16]. It may be worth mentioning that Das and Das

Table 4 Equilibrium moisture content of "PVP-CMC" hydrogel film at different temperatures and relative humidities

Temperature (°C)	Water activity	[a]EMC (% db) ± SD
25 °C	0.087	17.662 ± 0.75
	0.237	19.682 ± 0.93
	0.327	23.567 ± 1.11
	0.443	25.608 ± 0.76
	0.536	27.621 ± 1.07
	0.742	39.797 ± 0.93[b]
	0.752	39.581 ± 2.62[b]
	0.855	58.043 ± 1.95
	0.972	118.693 ± 1.16
	$LSD_{0.05}$	1.48
	$LSD_{0.01}$	2.13
35 °C	0.065	19.985 ± 1.22[b]
	0.215	23.085 ± 3.03[b]
	0.320	23.286 ± 0.85[b]
	0.436	39.739 ± 0.97
	0.515	25.33 ± 1.13[b]
	0.720	35.667 ± 0.87[b]
	0.748	39.295 ± 0.77[b]
	0.822	53.090 ± 1.17
	0.967	119.196 ± 26.76
	$LSD_{0.05}$	11.33
	$LSD_{0.01}$	16.34
45 °C	0.050	37.941 ± 2.17
	0.197	11.054 ± 0.40[b]
	0.311	15.704 ± 0.95[b]
	0.429	32.701 ± 4.72
	0.497	20.115 ± 0.78[b]
	0.699	25.925 ± 1.68[b]
	0.745	29.873 ± 2.47[b]
	0.791	36.071 ± 0.48[b]
	0.968	168.022 ± 15.77
	$LSD_{0.05}$	7.09
	$LSD_{0.01}$	10.22
55 °C	0.039	24.237 ± 1.66
	0.182	16.267 ± 2.84[b]
	0.300	17.702 ± 1.38[b]
	0.424	23.090 ± 2.12[b]
	0.481	26.970 ± 4.80[b]
	0.686	27.532 ± 3.66[b]
	0.71	30.745 ± 5.75[b]
	0.764	30.504 ± 0.85[b]
	0.965	70.575 ± 1.81
	$LSD_{0.05}$	5.75
	$LSD_{0.01}$	3.99

[a]Mean of five replications ± SD, for each temperature, F-test is positive ($p < 0.01$) on EMC for variation of a_w.
[b]Within a column, the two consecutive values are not significantly different (LSD test, $p > 0.05$).

Table 5 Constants and fitting parameters for "PVP-CMC" hydrogel film at different temperatures using GAB, BET, and Peleg models

Model	Parameter	Temperature			
		25 °C	35 °C	45 °C	55 °C
GAB	M_0	14.266	14.244	9.777	13.323
	C	1.30E + 45	8.62E + 44	−1.05E + 46	−3.12E + 45
	K	0.903	0.908	0.978	0.841
	R^2	0.991	0.953	0.938	0.899
	RMSE	2.71	6.38	11.25	4.81
	MRE (%)	7.31	13.38	23.05	13.53
	Residual plot	Pattern	Pattern	Pattern	Pattern
BET	M_0	3.669	4.408	6.596	3.573
	C	7.54E + 45	−2.16E + 45	−4.49E + 46	−4.10E + 46
	R^2	0.528	0.589	0.921	0.161
	RMSE	26.80	27.65	13.24	12.30
	MRE (%)	80.91	85.84	32.24	33.11
	Residual plot	Pattern	Pattern	Pattern	Pattern
Peleg	K_1	105.292	115.869	211.970	63.626
	n_1	8.188	9.322	10.867	6.181
	K_2	34.348	34.714	23.835	21.383
	n_2	0.322	0.252	4.68E-15	1.81E-14
	R^2	0.993	0.978	0.971	0.970
	RMSE	2.65	4.77	8.47	7.66
	MRE (%)	5.77	7.57	33.73	27.67
	Residual plot	Random	Random	Random	Random

Table 6 Constants and fitting parameters for "PVP-CMC" hydrogel film using modified Oswin model

Model	Parameters	Values
Modified Oswin	A	33.748
	B	−0.135
	x	2.306
	R^2	0.921
	RMSE	18.99
	MRE (%)	29.22
	Residual plot	Pattern

reported that food rich in soluble solid may show increase in EMC with increase of temperature, as observed here for the range of 25–35 °C [30]. Onward at a_w of 0.8, EMC, however, exhibited crossover phenomenon showing highest at 45 °C. Such type of crossover was also reported by Chowdhury and Das [12] as well as Sen [14].

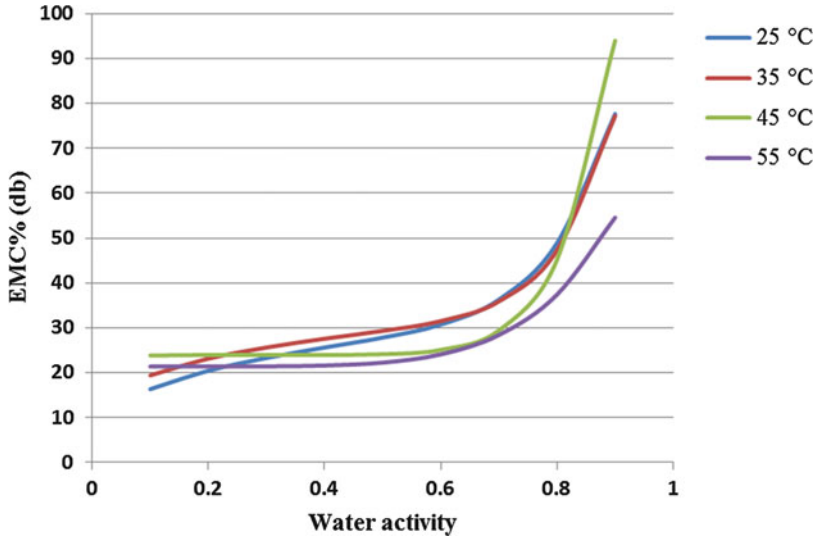

Fig. 4 Effect of temperature on moisture sorption isotherm of "PVP-CMC" hydrogel film

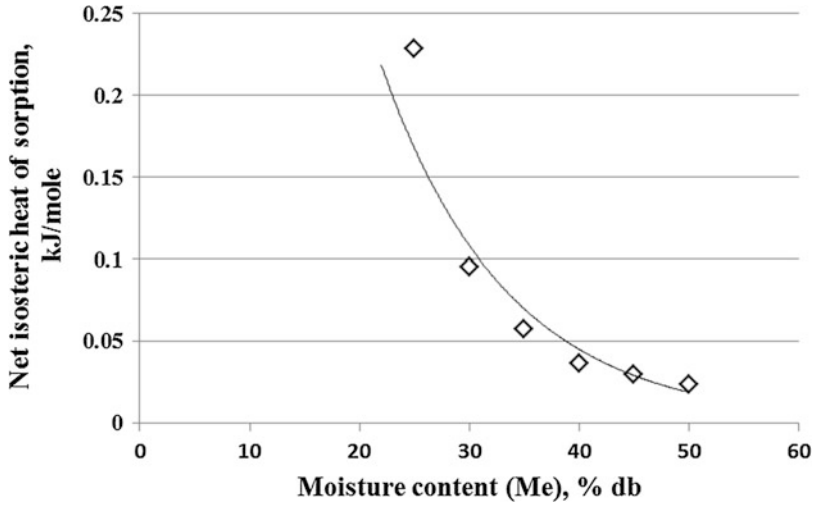

Fig. 5 Net isosteric heat of sorption of "PVP-CMC" hydrogel film at different moisture contents

3.2.4 Net Isosteric Heat of Sorption

The variation in net isosteric heat of sorption (q_{st}) with equilibrium moisture content (25–50%, db) is shown in Fig. 5. The figure reveals that q_{st} decrease exponentially with increase in moisture content following the relation as showed in Eq. (5) with $R^2 = 0.930$.

$$q_{st} = 1.4985\ \mathrm{Exp}(-0.088\ M_e) \quad (5)$$

where "M_e" represents moisture content (%db) of the film. According to Tsami [31], for any absorbing surface, the higher the value of q_{st}, the higher is the degree of binding. Therefore, this exponential relationship suggests that binding sites are heterogeneous in nature for this film.

4 Conclusion

The "PVP-CMC" hydrogel film is transparent, flexible, nontoxic, sealable, and self-supporting. The film is biodegradable and breathable and shows significant mechanical properties. The "PVP-CMC" hydrogel film, when tested for food packaging, could successfully extend the shelf life of respiring food items like table grape.

The film in dry condition could absorb water molecules in the vapor phase. The amount being 40–50% (db) in up to around 80% RH environment. The Peleg model could sufficiently describe the water sorption. The binding sites were heterogeneous in nature, and above 50% moisture content the bound moisture behaved as good as free water with net isosteric heat of sorption (q_{st}) gradually approaching to zero kJ/mole.

5 Future Scope

As the "PVP-CMC" hydrogel-based food packaging material showed several advantageous properties especially for the fresh fruits, vegetables, and the food stuffs which release moisture, there is ample scope for further investigation to perform a case study using this hydrogel food package for individual fresh fruits and vegetables like green chilli, grape, tomato, spinach, etc.

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Cellulose-Based Hydrogels for Pharmaceutical and Biomedical Applications

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Abstract

Hydrogels, the hydrophilic polymers, exhibit a three-dimensional network that can swell and retain the water molecules or any liquid in its structure, ten to 1000 times higher than its normal weight. The chemical cross-linking, physical entanglement, hydrogen bonds, and the ionic bonds are responsible to achieve the network of hydrogels. Hydrogels based on natural polymers like chitosan and cellulose are of great interest because of their abundant availability and biocompatibility and biodegradability. Natural polymer-based hydrogels have been used extensively in biomedicine, bioengineering, agriculture, and horticulture such as drug delivery, food, cosmetics, high water-absorbing resin, contact lenses, corneal implant, and substitutes for the skin, tendons, ligaments, cartilage, and bone due to their excellent hydrophilicity, permeability, compatibility, and low friction coefficient. Hydrogels specially cellulose ethers possess a remarkable combination of important properties for pharmaceutical and biomedical applications, e.g., as carriers for drug targeting, sustained release of drugs, vaccine bullets, and materials for the disintegration of matrix tablets. For the treatment of severe skin burns and in the regeneration of cardiac, vascular, neural, and cartilage bone tissues, these cellulose derivatives are very useful. In this regard bioactive hydrogels can be properly designed to induce at least partial skin regeneration. Cellulose-based hydrogels cross-linked with hyaluronic acid induce a good proliferation of keratinocytes, as a result of a scratch wound model in in vitro culture. Literature data have proposed the use of CMC- and HEC-based hydrogels as water absorbents in treating edemas. Hydrogels are also used as water absorbents for various applications in personal hygiene products or as biomedical devices, like soft contact lenses, lubricating surface coatings, phantoms for ultrasound-based imaging, etc.

Keywords

Hydrogels · Biocompatibility · Controlled drug delivery · Biomedical application · Pharmaceutical applications

1 Introduction

Hydrogels can swell and retain a large amount of water within its structure [1] due to its three-dimensional network of hydrophilic polymers. Hydrogels are most promising materials in biomedical field due to their variety of composition, fabrication, and flexibility in physical, chemical, and biological properties, especially their excellent biocompatibility and similarity to native extracellular matrix (ECM). So they are very important materials in the field of academic research [2–6]. The chemical cross-linking [7], physical entanglement [8], hydrogen bonds [9], and ionic bonds [10] are responsible to achieve the network of hydrogels. Due to their excellent hydrophilicity, permeability, compatibility, and low friction coefficient, polymer-based hydrogels have been used extensively as drug delivery, food,

cosmetics, high water-absorbing resin, contact lenses, corneal implant, and substituents for the skin, tendons, ligaments, cartilage, and bone [11, 12]. In cases where sharp and/or fast swelling and de-swelling transitions happen in response to change of external stimuli, hydrogels are potentially useful for the development of a variety of smart devices, such as valves, artificial muscles, and substrates for controlled drug release [13–15]. Some of the hydrogels can change their shapes, structures, and properties significantly and reversibly in the presence of external stimuli such as pH value, temperature, ionic strength, enzymatic activity, glucose concentration, light, electric field, magnetic field, pressure and solvent composition, or a combination of them [16–18]. The volume or mass swelling ratio of the hydrogel is the most important variable to be evaluated for given environmental conditions, as it affects the diffusive, mechanical, optical, acoustic, and surface properties of the hydrogel itself. Furthermore, an exclusive class of hydrogels – super-porous hydrogels – can potentially be used for both short- and long-term applications, as super dis-integrant, controlled release platform and a gastro-retentive drug delivery system. Also, super-porous hydrogels have been successfully used as soil improvers [19], slow-release fertilizers [19, 20], and pesticide release devices [21]. The first hydrogels based on poly(hydroxyethyl methacrylate) (PHEMA) developed by Otto Wichterle in the 1950s and later patented for use as soft contact lenses [22]. Instead of using the PHEMA in hydrogel matrix, there are other synthetic polymers used for preparation of hydrogels by polymerization or cross-linking method, like poly(ethylene glycol) (PEG), poly(vinyl alcohol) (PVA), polyacrylic acid (PAA), poly[N-(2-hydroxypropyl) methacrylamide] (PHPMA), polyvinylpyrrolidone (PVP), polyurethanes (PU), polyacrylamide (PAM), poly(N,N-dimethylaminoethyl methacrylate) (PDMAEMA), and poly (N-isopropylacrylamide) (PNIPAM) as well as polypeptides and polyesters. Further great steps have been taken by researchers toward obtaining novel hydrogels, based on synthetic, natural, or hybrid polymers, which possess given swelling properties and/or biocompatibility and bioactivity. Natural hydrogels are generally interacting to the cell and have a property of cell adhesion and cell signaling for their biocompatibility and biodegradability. These hydrogels are prepared from many natural sources like chitosan (CS), hyaluronic acid (HA), gelatin (GEL), collagen (COL), alginate (ALG), elastin (ELA), heparin (HEP), and chondroitin sulfate (CRS), being appealing for biological and biomedical applications [23–25].

2 Cellulose and Cellulosic

The most abundant naturally occurring biopolymer is cellulose [26, 27]. Cellulose is the main constituent of various natural fibers such as cotton and higher plants [28, 29]. In cellulose we have a long chain of anhydro-D-glucopyranose units (AGU). Each cellulose molecule has three hydroxyl groups per AGU, with the exception of the terminal ends. These celluloses and its derivatives are strong, reproducible, and biocompatible. Thus they have opened a window of opportunity to be used in biomedical and pharmaceutical fields [30].

2.1 Oxidized Cellulose (Oxycellulose)

In oxycellulose some of the alcohol groups at the terminal are converted into carboxyl group. 25% of these carboxyl groups are too brittle (friable) and too readily soluble to be of use, and they are synthetic poly-anhydrocellobiuronide. These oxidized cellulose fabrics are used in cotton or in gauze as they are insoluble in water or in acid. In slightly alkaline medium, it swells forming a sticky brown gelatinous mass. So it can be used directly in surgical procedures to the oozing surface except when used for homeostasis. While cellulose disperses in water, it forms a thixotropic dispersion. The acidic, neutral, or basic bioactive solid or liquid compounds thus can be entrapped in such moiety which can apply in various cosmetics, pharmaceutical, agricultural, and consumer products. Being bioadhesive, oxycellulose are also applied on human skin or hair [31] and used as anti-acne cream, anti-acne lotion, sunscreen spray, and antifungal cream.

2.2 Microcrystalline Cellulose

Microcrystalline cellulose (MCC) is advantageous for using in the formulation of solid dosage forms. But it has some drawbacks like low bulk density, moderate flow ability, loss of compatibility after wet granulation, and sensitivity to lubricants. These can be overcome by silicification of MCC (SMCC) which improves the functionality of MCC with such properties as enhanced density, low moisture content, flow ability, lubricity, larger particle size, compatibility, and compressibility [32], due to the inter-surface interaction with MCC. Silicon dioxide adheres to the surface of MCC and shows higher bulk density and tensile strength comparative to the common type of MCC [33, 34]. A study revealed that SMCC exhibited relatively higher compatibility under the low compression force of a donator capsule filling than either poly(glycerol sebacate) (PGS) or lactose. The SMCC materials loaded with 5% piroxicam and 30% and 50% acetaminophen respectively, show higher compatibility under the low compression force and faster dissolution rates than those formulated with PGS and anhydrous lactose. Thus SMCC can be a suitable alternative excipient for direct-fill formulations for hard shell capsules [35]. The size and weight of individual tablets were also decreased, which increases patient's compliance [36].

A study revealed that a large number of tablets can be manufactured in substantially cheaper method due to decreased size, higher compressibility, and better flow properties (lower sensitivity to the rate of tableting) of SMCC [37]. In the presence of sodium stearyl, high-density SMCC are more sensitive to the addition of lubricants, and a greater decrease in strength has occurred. The disintegration time of mixture from SMCC is shorter and increased with increasing compression force with or without lubricants.

2.3 Cellulose Ethers

Cellulose ethers are vastly used as important excipients for manufacturing the matrix tablets. In the presence of water, the cellulose ethers start to swell forming the dry

core of hydrogel around the tablet. The hydrogel acts as a diffusional barrier for water molecules which penetrate into the polymer matrix and the drug molecules being released [38–40].

2.4 Sodium Carboxymethyl Cellulose

Sodium carboxymethyl cellulose (NaCMC) is a polyanionic polysaccharide derivative of cellulose and commercially available as low-cost materials. It can be used in medicine, as an emulsifying agent in pharmaceuticals, and in cosmetics [41]. For their important properties, this polymer can act as a preferred thickener, suspending aid, stabilizer, binder, and film former in a wide variety of uses. In biomedicine, for preventing postsurgical soft tissue and epidural scar adhesions, CMC is used.

Sanino et al. have studied the effect of CMC- and HEC-based hydrogels in the treatment of edemas [42]. In therapeutic application, CMC carries the superoxide dismutase (SOD) enzyme for its controlled release [43]. The SOD enzyme can mix with CMC as conjugates or as hydrogels after absorbed in the hydrogel matrix. Both are chemically characterized, expressing the result that up to 50% of the SOD was released from the SOD-CMC hydrogel after 72 h, indicating a controlled release kinetic [44].

CMC-containing substitute and a glycerin mouthwash are given, as a control, to the patients suffering from Sjogren's syndrome. CMC-containing substitute can relieve more nocturnal oral discomfort [45]. In a comparative studies it was observed that two saliva substitutes, one containing mucin and other containing CMC, have the same effects with changed friction values of about 15 min which was more than twice as long as for water. For the preparation of semi-interpenetrating polymer network microspheres, NaCMC was also used where glutaraldehyde acts as a cross-linker. In this microsphere for example, ketorolac tromethamine, an anti-inflammatory and analgesic agent, was successfully encapsulated and up to 67% encapsulation has occurred. Another nonsteroidal anti-inflammatory agent is indomethacin. It has a short biological half-life of 2.6–11.2 h [46]. The usual oral dosage of this medicine for adults is 25 or 50 mg, 2–3 times a day [46]. If the drug is released in a controlled manner, it will help patient to reduce adverse effects, fluctuation in plasma concentration, and dosing frequency. According to Waree and Garnpimol, a complex of chitosan and CMC which was cross-linked by glutaraldehyde can control the release of indomethacin from microcapsule [47]. Glutaraldehyde reacts with the hydroxyl group of CMC chain forming acetal and amino group of chitosan forming a Schiff base. Due to the cross-linking, the composite forms a dense and rigid surface of microcapsule reducing the degree of swelling and thus controlling the drug release. Esterification of NaCMC with acryloyl chloride was done to enhance the swelling property by changing the pH. At pH of 9.4, the swelling % is quite high compared to that at pH 1.4 and 5.4. Thus this polymer composite can be used as pH-responsive polymer in biomedicine, as controlled drug delivery system for aspirin, indomethacin, diclofenac, etc. in the intestine, and as a wound dressing material [48]. As this polymer can swell in high pH and reduce in low pH, it can be used in oral drug delivery system also.

2.5 Methylcellulose

Methylcellulose (MC) swells in water, forming a clear to opalescent, viscous, colloidal solution. In most of the common organic solvents, methylcellulose is insoluble. Over a wide range of pH (2–12), MC is the most stable substance with no apparent change in viscosity. Thus they are suitable as bulk laxatives and can be used to treat constipation or used in nose drops, ophthalmic preparations, burn preparation ointments, and other preparations. The hydroxyl group present in MC structure can interact with the carboxylic acid group of carboxyvinyl polymer (CP), as well as with poly(ethylene oxide) (PEO). Ozeki et al. examined controlled release of the drug, antipyretic phenacetin (PHE), from solid dispersion of an inter-polymer complex between MC and CP. It was observed that the release of drug depends upon the formulation; either it was solid dispersion of granules or it was PHE powder. The rate is lower for the first case. From this study it was confirmed that the release of PHE from MC-CP complex can be modified by complex formation maintaining the various ratios of MC/CP and the molecular weight of MC [49].

2.6 Ethyl Cellulose

Ethyl cellulose (EC) is insoluble in water and can be soluble in many organic solvents. Thus it is a non-swellable and insoluble substance in the matrix or coating systems. In some cases the water-soluble binders cannot be used in dosage processing for their water sensitivity of the active ingredients. So these hydrogels are used as a coating material for that active ingredient of tablets, so that they cannot interact with other materials. It allows granulations for easily compressed tablets and other dosage forms. This can be used frequently on its own form or mixed with water-soluble polymers as a film to coat microparticles, pellets, and tablets. According to many researchers like Mura et al. [50], Friedman and Golomb [51], and Soskolne et al. [52], EC can also be used to sustain the drug release. In addition to EC, hydroxyethylcellulose (HEC) is also used as a modified release tablet matrix, a film former, a thickener, and a stabilizer. This is a suspending agent for oral and topical applications when a nonionic material is desired.

2.7 Hydroxypropyl Cellulose

Hydroxypropyl cellulose (HPC) is a water-soluble and pH-insensitive material suitable for the application as thickening agent, tablet binding, modified release, and film coating. It can be more effective to control the release of a drug such as oxprenolol hydrochloride which is water soluble by mixing with EC to form a solid dispersion [53–55]. These indicate that the rate of release of water-insoluble drug is related to the interaction with the polymer [56–58]. For buccal delivery formulations, the mixture of polymers, HPC, and polyacrylic acid in different ratios is used from many years [59], but there are very few reports published where this polymer is

used in the treatment of oral mucosal disorders such as canker sores. To enhance the biocompatibility with high molecularity, swelling behavior, hydrophilicity, and physical and chemical properties, HPC was blended with hydroxypropyl starch. Into this matrix hydroxypropyl methacrylate was incorporated by Ce(IV) redox initiation method, and ethylene glycol dimethacrylate was used as cross-linker. Rheological studies suggested that this graft copolymer is very much suitable for the controlled drug delivery method. Although the non-cross-linked copolymer of hydroxypropyl methacrylate matrix with HPC or with hydroxypropyl starch offers interesting characteristics as controlled release matrices.

2.8 Hydroxypropyl Methylcellulose

Hydroxypropyl methylcellulose (HPMC) is a water-soluble cellulose ether. Thus it is suitable for the preparation of controlled release tablets as hydrophilic polymer. In the presence of water molecules, the polymeric chain is hydrating, promoting the disentanglement of polymeric chain from matrix. Reynolds et al. observed that the controlled release of drug by polymer erosion method is dependent on time and a function of the number average molecular weight of the polymer (HPMC). Generally polymer erosion was found to be inversely related to the polymer number average molecular weight [60]. The rate limiting step for polymer erosion method is the diffusion of polymer (HPMC) chains from aqueous diffusion layer. In addition the ratio of surface area and volume is also a parameter of controlled release of tablets from HPMC matrix. It is also utilized to duplicate drug release profiles for tablets which have different sizes, shapes, and dose levels.

Ifat Katzhendler et al. examined how the controlled release of the drugs like naproxen sodium (NS) and naproxen (N) was dependent on the molecular weight of HPMC [61]. In spite of the difference in their molecular weight, HPMC is characterized by the same microviscosity values, where the matrix is composed of various viscosity grades of HPMC. Incorporation of naproxen in the HPMC matrix lowers the internal pH value inside the hydrated tablet compared to that incorporation of NS. Due to the lower solubility of N, it dominates the surface erosion mechanism, whereas NS is characterized by higher internal pH value and higher drug solubility. According to Khanvilkar et al., the mixture of two different grades of HPMC affects the apparent viscosity on drug release profile. The lower and higher viscosity grades of HPMC can be mixed uniformly in definite ratios to get the desired result. If we use low viscosity grade of HPMC, it will cause shorter lag (lag time, the time taken by the matrix tablet edges to get hydrated and achieve a state of quasi-equilibrium before erosion and the advance of solvent front through the matrix occur). Ye et al. have studied the distribution of HPMC in the tablet matrix and concluded that manufacturing procedure is very important factor to determine the dissolution characteristics of HPMC matrix tablets. The tablet hardness, the distribution of HPMC within the tablet (intergranular and intragranular), and the amount of water added in the wet granulation step are the important factors of dissolution while HPMC matrix tablets were prepared by wet granulation method. If HPMC are

embedded in partial amount intergranularly in the dry-blend step, drug release profiles could be much less sensitive to the manufacturing process [62].

Liu et al. used alginate as gelling agent in combination with HPMC which acted as the viscosity-enhancing agent in release of gatifloxacin. It was evident from both in vitro release and in vivo pre-corneal retention studies that the alginate/HPMC solution retained the drug better than only HPMC or alginate. The alginate/HPMC matrix can be applied as an in situ gelling vehicle to enhance ocular bioavailability and patient compliance [63]. HPMC provides the properties of hydration and gel formation which is helpful to prolong release of active compound like yahom. Yahom is a well-known traditional remedy/medicine for treatment of nausea, vomiting, flatulence, and unconsciousness in Thailand [153]. Chantana et al. found that the higher amount of polymer, HPMC, will enhance the disintegration time of the tablet. So, the tablet containing 50% yahom, having the polymer mixture of PVP and HPMC in the ratio of 1:2, was suitable to use as the buccal tablet since it has the low water sorption and erosion property. In these cellulose derivatives, amylose starch (CLA) is used as a cross-linking agent and serves as a controlled release excipient for the preparation of solid dosage forms [64]. The swelling behavior and erosion of granulated cross-linked high amylose starch (CLAgr)/HPMC tablets will increase with the increase in HPMC concentration and incubation time. Some of the experiments revealed that the release of both pseudoephedrine and diclofenac sodium was more rapid from CLAgr, CLAgr/HPMC, and granulated CLA/HPMC tablets than HPMC matrices in absence of α-amylase. If the amount of HPMC is 10% in CLA matrix, it will reduce the enzymatic hydrolysis by slowing down the diffusion of the enzyme in the substrate. However, this was less significant for highly water-soluble drugs, such as pseudoephedrine, which diffuses rapidly out of the matrix. In another study of concentration of HPMC versus release of the drug naproxen, it was shown that the increased amount of HPMC resulted in a reduced drug release. The incorporation of sodium bicarbonate and calcium carbonate in the HPMC matrix enhanced the naproxen dissolution.

Hydrophilic matrix system is restricted for use in extended drug release for the water-soluble drugs due to rapid diffusion of the dissolved drug through the hydrophilic gel network. For these water-soluble drugs, hydrophobic matrix is more preferable, which can sustain the release dosage forms [65]. Hydrophobic matrix is advantageous as it is stable from a wide range of pH and moisture level to well-established safe applications. Sandip et al. compared the effect of hydrophobic polymer (hydrogenated castor oil [HCO] and EC) with the hydrophilic polymer (HPMC) on controlled release of the drug tramadol. The result indicates that the hydrophobic matrix tablets resulted in sustained in vitro drug release (>20 h) as compared with hydrophilic matrix tablets (<14 h). Some study revealed that EC/HPMC combination is exhibiting higher concentration of hydrophilic part, increasing the release rate, kinetic constant, and diffusion coefficient. But for HPMC/BW, HPMC/CA, and HPMC/SA combinations, with the increase in hydrophobic part of the blend system, substantial reduction of release has occurred [66]. Vueba et al. studied the release of ibuprofen by using both low and high viscosity grade MC or HPC and HPMC, respectively. The result showed that mixing of both low and high viscosity grade cellulose ether polymers uniformly in different ratios modulates the drug release property.

2.9 Cellulose Esters

Cellulose esters like cellulose acetate phthalate are a partial acetate ester of cellulose, when reacted with phthalic anhydride. One of the carboxyl groups of the phthalic acid is esterified with the cellulose acetate. The acidic form is soluble in organic solvents and insoluble in water. The salt formed is readily soluble in water. This combination of properties makes it suitable for enteric coating of tablets due to its resistance to the acidic condition of the stomach but solubility in the more alkaline environment of the intestinal tract [67].

3 Composites of Hydrogels and Nanoparticles

Both the three-dimensional hydrogels and nanoparticles (NPs) are exhibiting some of the unique structures and properties which are very much suitable for medical therapeutic and diagnostic applications. But there are some inherent limitations of hydrogels and NPs interfering their wide spread applications. Hydrogels are having limited functionalities and inferior mechanical properties which are not fit for the demand of multifunctional hydrogel with enhanced mechanical property. On the other hand, NPs, having plenty of unique multifunctionalities for biomedical applications, are unstable, and their low biocompatibility and opsonization activity provide significant clinical challenges. To meet the rigorous requirements for biomedical use, various strategies have been applied to overcome the drawbacks, maintaining the advantages of hydrogels and NPs. Thus NPs are incorporated in the hydrogel matrix to prepare a novel compound with various functionalities removing the challenges in properties. These nanocomposite hydrogels are of great interest for various biomedical applications due to enhancing the characteristics of a nano-particulate material (e.g., very small size and high surface area) with hydrogel system (e.g., hydrophilicity and extremely high water content) [68]. The NPs are incorporated into the matrix to increase the mechanical property of hydrogels. Usuki et al. incorporated montmorillonite, a type of natural silicate mineral ("clay") NPs, into nylon-6 network, which significantly improved the tensile strength of hydrogels [69]. The inorganic clay NPs also showed hydrophilicity and solubility when they are dispersed into 3D polymer networks. Thus the new substance provides essential requirements for the reasonable wound dressing with some desirable characteristics [70]. With incorporation of NPs in hydrogel moiety, some of the physicochemical properties will be imparted by the novel molecule. For example, the incorporation of Au or AgNPs in a polymer matrix will show excellent antimicrobial property [71]. Similarly the use of magnetic NPs in hydrogel matrix will make the substance magnetic.

A wide range of NPs like carbon-based nanomaterials (carbon nanotubes (CNTs), graphene, fullerene), inorganic/ceramic NPs (silica, silicates, clay, hydroxyapatite, calcium phosphate, quantum dots (QDots), metal/metal oxide nanoparticles (gold, silver, copper, platinum, iron oxides, and titanium oxides), and organic NPs (polymer NPs, micelles, polymersomes, dendrimers, and liposomes) can be used within

the hydrogel networks to obtain nanocomposite hydrogels with enhanced functionality and superior physicochemical and biological properties.

3.1 Nanocomposite Hydrogels from Hydrogels and Carbon-Based NPs

Hydrogels, generally prepared from a single or multiple polymer networks, do not have all the important mechanical properties for tissue engineering. They also lack functions (such as electrical, optical, and thermal conductivity) for use in controlled drug delivery or bio-sensing and bio-imaging. Therefore some of the molecules are embedded in the hydrogel polymeric network to improve the properties [72, 73]. Carbon-based NPs, such as carbon nanotubes (CNTs), graphene, and fullerene (C60), exhibit interesting properties like mechanical strength, corrosion resistance, low cost, and environment-friendly nature, especially thermal, electrical, and optical conductivity and excellent multifunctional feature. Thus these NPs are incorporated into the hydrogel for enhancing their properties applicable for tissue engineering [74, 75]. As a novel reinforcing agent in polymer matrix, for biomedical applications, various carbon-based NPs like graphene-based materials (including graphene, graphene oxide (GO), and reduced graphene oxide (rGO)) are extensively explored. Graphene often causes a high difficulty in processing and low compatibility with polymer matrices due to its hydrophobic nature. In contrast GO has various oxygen-containing groups such as epoxide, carbonyl, carboxyl, and hydroxyl groups and thus can disperse in water or alcohol by hydrogen bonding. Undoubtedly, these graphene-based materials into hydrogel network are extremely important to increase the mechanical and thermal properties of the hydrogels. Normally, the graphene sheets have sharp edges, which can penetrate through cell membranes. Though the sharp edges also enhance the cytotoxicity [76]. The incorporation of graphene in a water-rich environment of hydrogels can change its interaction with cells and thus serves as a solution to prevent this effect. Carbon-based NPs having excellent optical, thermal, and electrical conductivity increase the conductivity of stimuli-responsive hydrogels and are highly promising [77, 78]. By incorporating carbon-based NPs in hydrogel, it can become optical or electrical-responsive nanocomposite hydrogels which are commonly used as actuator, biosensor, or tissue engineering scaffold (Table 1).

3.2 Nanocomposite Hydrogels from Hydrogels and Inorganic NPs or Semiconductor NPs

Some of the inorganic NPs like silicon-based NPs and quantum dots (QDots) are also used vastly for incorporating in the polymeric chain to synthesize a novel composite with unique properties and functions. Silicon-based NPs, including silica NPs (SiO_2), meso-porous silica NPs (MSNs), hydroxyapatite (HAP), and bioactive glasses as well as various kinds of clay (such as montmorillonite (MMT), laponite

Table 1 List of carbon nanomaterial-based hydrogels and their application in biomedical field

SL. no.	Carbon-based nanoparticles	Application
1.	CNT	1. In PVA, P(AM-co-EBA), MPEG/α-CD, BC/SA, PEI-fc: Controlled drug delivery, improve electrical conductivity and antibacterial effect
		2. In PHEMA, PNIPAM, P(EGDMA-co-HEMA), DNA, GEL: Applicable in tissue engineering
2.	Graphene	1. In PVA/P(MA-co-NIPAM), β-CD /PDMA: Controlled drug delivery, improve electrical conductivity and antibacterial effect
		2. In bacterial cellulose, CS/GEL: Applicable in tissue engineering
3.	Graphene oxide	1. In PEG, PLA-PEG-PLA, PEGDGE: Controlled drug delivery, improve electrical conductivity and antibacterial effect

(LAP), attapulgite, and halloysite), can be used as a significant nonfiller in nanocomposite hydrogels. Among these NPs, most of them are present in human body and have various functionalities in the human tissues [79]. Thus silicon is a very important material in skeletal development promoting the collagen type I synthesis and increases the osteogenic differentiation in human stem cells [79]. The simple polymer hydrogels are poor in mechanical strength and cannot induce the mineralization process. Thus the silicon-based nanoparticles and nanoclays are embedded in hydrogel network to enhance the mechanical property and biocompatibility for the repair and regeneration of human tissues and body functions. While nanoclays are incorporated in hydrogel network, a non-covalent surface interaction is taking place between the nanoclays and polymer chains due to the anisotropic and platelike, high aspect ratio of the nanoclays. These multifunctional hybrid hydrogels can be prepared via sol-gel method applicable for minimally invasive therapies, such as injectable tissue repair matrices or bone-related tissue engineering scaffolds [80, 81]. Some silicon-based NPs, especially MSNs, MMT, and LAP, having an ability to carry drugs are widely applicable to integrate into hydrogel drug delivery systems to increase drug loading, manipulate drug pharmacological profiles, minimize drug degradation, and decrease detrimental drug side effects [82]. Hence these bioactive hydrogel nanocomposites exhibit interesting mechanical property, good biocompatibility and biodegradability, enhanced tunable cell and tissue adhesion, or improved drug loading and drug release profiles. Thus they are very promising in biomedical and pharmaceutical fields, such as injectable or implantable sustained drug delivery system, controlled cell and tissue adhesion surfaces, antimicrobial films or wound dressings, tissue engineering, and cell-based therapies.

The dispersion of silica NPs in hydrogel matrix not only improves its mechanical skin adhesion and film-forming properties of PVA gels but also reduces the crystalline regions of PVA facilitating the diffusion of drug and water vapor.

The semiconductor quantum dots (QDots), such as CdTe, CdS, carbon, and silicon QDots, are of great interest for their unique photoluminescence behavior, including high quantum yield, large absorptivity, broad absorption spectrum, improved photostability, concentration, and size tunable emission [83]. The

fluorescent quantum dots are thus used for imaging live cells all the way, determining the location of proteins and the cellular structure bio-imaging in vivo, light-triggered drug delivery, immunoassays, and innovative diagnostic methodologies [84, 85]. These quantum dots are dispersed well and soluble and thus helpful in the biomedical applications, such as bio-sensing, bio-imaging, bio-labeling, and drug delivery. When the fluorescent quantum dots are mixed with hydrogels, it will protect the dots in unfavorable environment, showing improved photoelectronic properties that are highly suitable for therapeutic and diagnostic applications in biomedical fields [3]. For the preparation of this type of composites, polymer hydrogels, such as polyacrylamide (PAM), poly(ethylene glycol) (PEG), poly (vinyl alcohol) (PVA), polyvinylpyrrolidone (PVP), COL, and AGL, are widely used to entrap the dots. The entrapment of quantum dots in hydrogel matrix is mainly dependent on the electrostatic interactions, hydrophobic interactions, hydrogen bonding, and host-guest interactions.

3.3 Nanocomposite Hydrogels from Hydrogels and Metal NPs or Metal Oxide NPs

There are various types of metals and metal oxides that are used to blend in the hydrogel moiety through covalent and non-covalent interactions forming a unique nanocomposite hydrogel. These metal and metal oxides possess various useful characteristics which we cannot find in any hydrogel polymers. Thus the prepared nanocomposites are also exhibiting interesting tunable property [86]. It was observed that incorporation of these NPs in hydrogel matrix through covalent manner will cause remarkable change in mechanical properties and swelling behavior of polymer nanocomposites. There are many metallic NPs, such as gold (Au), silver (Ag), platinum (Pt), cobalt (Co), nickel (Ni), and copper (Cu), and a series of metal oxide NPs including iron oxide (Fe_3O_4, Fe_2O_3), titanium dioxide (TiO_2), zinc oxide (ZnO), cupric oxide (CuO), as well as metal alloys and salts with desirable physicochemical properties which can be embedded in the synthetic or natural polymer matrix for designing diverse biomedical and pharmaceutical applications like biological sensing, in vivo bio- imaging, cell separation, drug delivery, conductive scaffolds, switchable electronics, and disease treatment. Among the nanoparticles, AgNPs are very remarkable for their antimicrobial activity and low toxicity for human cells [87]. But due to the strong dipole-dipole interaction, they are less stable and less dispersed, which limited their applications.

In hydrogel matrix, so many free spaces are there where the NPs are easily confined in the matrix and also the polymer network is acting as a nanoreactor template for the nucleation and growth of NPs [88]. If AgNPs are mixed with hydrogels, they exhibit high antibacterial activity, and usually some of the physical properties are changed like mechanical toughness, swelling ratio, and stimuli responsiveness. Due to the biocompatibility of hydrogel molecules, maintaining the moist environment at the wound surface, it can act as a barrier for microorganisms. Sufficient amount of air and water vapor can penetrate through the skin in the

presence of such hydrogel nanocomposites, which can also absorb or remove excess exudates, as well as attach at the target site and be easily removed without trauma and pain. AuNPs also have excellent optical and LSPR properties from the visible region to the near infrared (NIR), which is absolutely suitable for biomedical applications. The light wavelength of near IR region can penetrate the biological tissues with relatively little attenuation and minimal damage. Thus this is used widely for photothermal therapy (PTT), photodynamic therapy (PDT), bio-imaging, and remote-controlled smart drug delivery. Wang et al. prepared a hydrogel nanocomposite with AuNPs, spinach extract, and PEGDA following the method of photopolymerization. Here spinach extract, as photo-initiator, initiates the formation of PEGDA hydrogel which led to the formation of cytotoxic singlet oxygen $^1O_2$, after reaction with O_2 and can kill tumorous cells [89]. As a photo-absorbing agent, AuNPs can provide heat in the presence of optical energy to induce tumor tissue hyperthermia and accelerate the rate of $^1O_2$ generation. Thus the hydrogel nanocomposite shell prevents the tumor cell to migrate to the normal cells and keeps a high concentration on lesions, thereby enhancing the curative effect.

In some studies, magnetic NPs like ferrous (Fe), cobalt (Co), and nickel (Ni) are also used to incorporate in the hydrogel matrix offering a high potential for several biomedical applications, such as magnetic field-induced hyperthermia, magnetic resonance imaging (MRI), drug delivery, cell tracking, and protein separation. The iron oxide is supermagnetic material which can cause temperature rise in the presence of alternating magnetic field. Thus it can be used in the treatment of magnetic induction hyperthermia for cancer cell and cell biology. On the other hand, Liu et al. mixed the magnetic NPs in PVA matrix exhibiting the controlled on-off drug release property from the hydrogel composites. The controlled release of drugs is extremely monitored by particle size, strength of the magnetic field, and the duration of the switching time. Thus the release of drugs from the hydrogel moiety is remotely controlled in the presence of these magnetic NPs. Though there is less number of research work on the use of these magnetic NPs in hydrogel polymeric network, it has been done so far for their toxicity and rapid oxidation. Overall, various types of metallic and metal oxide colloidal particles are tried to incorporate in the polymer matrix enhancing exclusive optical, electrical, or magnetic properties of these compounds. So the modified nanocomposite hydrogels are highly promising in different biomedical applications, especially for diagnostic and therapeutic applications.

4 Biomedical and Pharmaceutical Application of Cellulose-Based Hydrogels

4.1 Superabsorbents for Personal Hygiene Products

Acrylate-based hydrogels are the superabsorbent, and thus it has vast use in personal care products like diapers and napkins, in drug delivery systems in pharmaceutical area, in catalysis, and in bio-sensing [90]. They keep moisture and wetness away

from the skin, which helps promote skin health and consumer comfort. These hydrogels are cross-linked polymer, which is insoluble in water. But it can absorb water through swelling process. Hydrogels can swell 10–10,000 times higher than its original initial weight. Several medical studies have provided clear evidence that disposable diapers play an important role in reducing the risk of spread of gastrointestinal illnesses and are significantly more effective than double cloth diapers and plastic over pants [91]. The disposal of diaper is a critical issue for environment as the cellulose is biodegradable but the plastic cover, SAP (superabsorbent polymer), is not.

An alternative solution to the problem of SAP recycling has been recently suggested and has been solved by the use of cellulose-based hydrogels, which are totally biodegradable. Cellulose-based products have been used for the absorption of water and other aqueous fluids in many cases, like the paper towels and tissue papers which are vastly used as absorbents. Fluff pulps, which are generally based on Kraft pulping and optimized for high bulk and absorbency products, are widespread use, e.g., disposable diapers [92]. Novel hydrogels, based on sodium carboxymethyl cellulose (NaCMC) and hydroxyethylcellulose (HEC), cross-linked with divinyl sulfone (DVS) are comparable with those displayed by SAP as they have also greater swelling capacity under centrifugal loads [93] (Fig. 1). These improvements were achieved by introducing microporous structures into the hydrogel, by means of a phase inversion desiccation technique in acetone, which increases water retention and swelling kinetics, due to capillarity effects. Comparing the scanning electron microscopy (SEM) images of an acetone-dehydrated vs. an air-dried cellulose-based hydrogel (Fig. 1), the surface of the former displays foldings and voids, whereas the latter shows a smooth and dense surface.

The swelling ratio (SR) is provided for acetone-dehydrated hydrogels (SEM micrograph A: red arrows indicate the voids or micropores) and air-dried ones (SEM micrograph B: smooth surface with no pores; exogenous white particles are likely due to air drying and manipulation). The values of SR in distilled water are also provided ($n = 5$) [94]. Thus the advantage of cellulose-based hydrogels over current SAP consists in their biodegradability and environment-friendly nature.

4.2 Controlled Drug Delivery

In pharmaceutical industry, cellulose ethers are generally used as the excipients in many drug formulations [95] and also can be used for oral, topical, or parenteral administration. Their use in solid tablets allows a swelling-driven release of the drug as physiological fluids come into contact with the tablet itself. Water-soluble cellulose derivatives are biocompatible and thus used in various fields like binding agents, emulsifiers, film formers, suspension aids, surfactants, lubricants, and stabilizers, especially as additives in food, pharmaceutical, and cosmetic industries. Due to the swelling nature of cellulose ethers on the tablet surface (e.g., HPMC), it starts to swell to form chain entanglement. While the swelling proceeds to form a glassy core of the tablet, the drug progressively dissolves in water defusing from polymeric chain. The cellulose derivatives are acting as enteric coating of the tablet or capsule

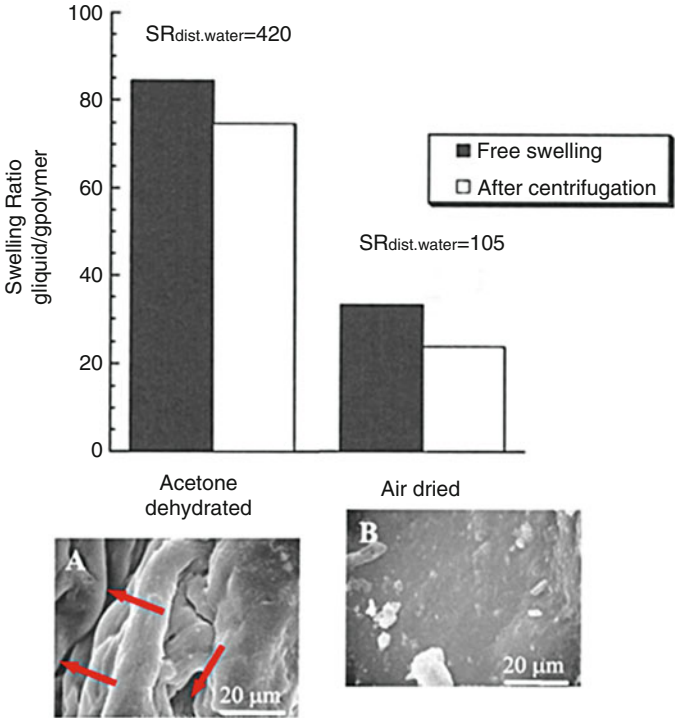

Fig. 1 Average uptake of synthetic urine by NaCMC/HEC hydrogels, both in free swelling conditions and after centrifugation [56]

and resistant to acidic environment, such as that of the stomach [96]. Moreover cellulose ethers have some interesting properties for which it can be used in pharmaceutical and biomedical applications, e.g., as carriers for drug targeting, sustained release of drugs, vaccine bullets, and materials for the disintegration of matrix tablets.

The mechanism of drug release follows the steps of swelling, diffusion, and erosion. It depends upon the swelling capacity as well as the cross-linking and the mesh size [97, 98]. Literature shows that, tablets prepared by compression of hydrophilic gums, excipients, and drug in specified ratios lead to prolonged release of drug. On account to this carboxymethylcellulose is an example of excipients, which sustain the release in solid oral dosage. Recently more advanced hydrogel-based celluloses are developed rather than only swelling tablets. The main aim of these cellulose derivatives is not only to be used for sustained release of a bioactive molecule over a long time period, but also site-specific, the affected organism, controlled release of drugs. These developed hydrogels controlled the time and site-specific drug delivery by their swelling and de-swelling transition method (Fig. 2). This process also related to the changes of pH, temperature, and ionic strength. The vast change in pH is taken place when the drug travels from the

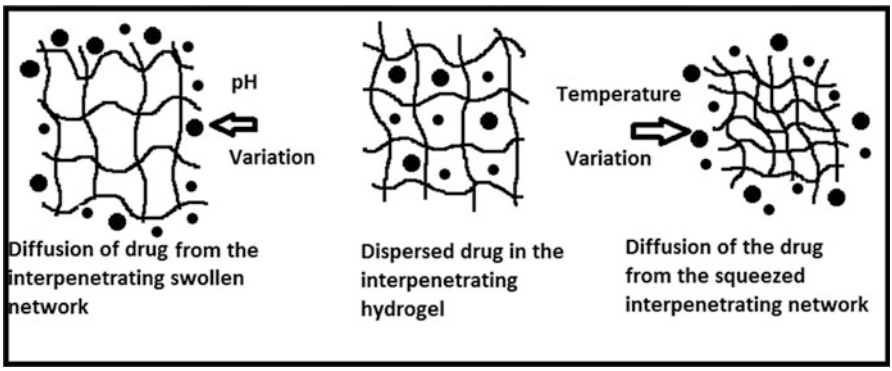

Fig. 2 Swelling and de-swelling behavior of interpenetrating hydrogel network

stomach to intestine [99]. In this context, cellulose-based polyelectrolyte hydrogels are appropriate for this application. Recently, literature data have developed anionic hydrogels based on carboxymethylcellulose for colon-targeted drug delivery.

The latest studies in controlled release of a hydrogel matrix refer to the proteins, growth factors, and genes to specific locations, used in tissue engineering applications. In order to avoid the interference of foreign particles in the body and after that the surgical removal of that particles, hydrogels should be biocompatible. Injectable hydrogel formulations are particularly appealing and currently under investigation. In a very mild condition the cross-linking reaction has to be done to prevent denaturation of loaded molecule. So significant progress has been made to enhance the property of cellulose-based hydrogels for drug delivery and expand the range of drugs and kinetics which can be realized using a hydrogel-based delivery vehicle. However, several challenges remain to improve the clinical applicability of hydrogels for drug delivery.

Dermal medicated cellulose-based hydrogels are developed to treat different problems with acute or chronic and mild or moderate skin conditions (i.e., eczema, dermatitis, psoriasis, acne, warts, inflammations, and allergies). These cellulose derivatives are obtained by dispersing the drug into the hydrogels or incorporating the drug in colloidal carriers like micro- and nano-emulsions, liposomes, niosomes, etc. to enhance the activity.

According to Kouchak and Handali [100], the in vitro permeation of aminophylline from 3% HPMC-based hydrogels through snake skin can be enhanced in the presence of sodium tauroglycocholate, lauric acid, and ethanol increasing the penetration property. From the reports of this research, sodium tauroglycocholate at concentration of 100 μg/ml and 60% ethanol are the optimum enhancers for aminophylline, intended to be used as anticellulitic agent. This can increase the permeation six times than in the normal condition.

The model drugs which are antifungal agents like clotrimazole, bifonazole, and fluconazole are first dispersed in emulsion or microemulsion systems and then incorporated in cellulose-based hydrogels to improve the viscosity of the emulsion,

Table 2 Overview of cellulose derivative-based hydrogels as vehicles for cutaneous delivery of drugs

Sl. No.	Controlled release of specific drugs	Cellulose derivative used	Hydrogels in pharmaceutical dosage form
1	Alaptide	HEC, HPC, MC	Hydrogel
2	Aminophylline	HPMC	Hydrogel
3	Bifonazole	HPMC	Microemulsion-loaded hydrogel
4	Clarithromycin	HPMC	Emulgel
5	Chlorphenesin	HPMC	Emulgel
6	Clotrimazole	HPMC	Emulgel
7	Diclofenac sodium	CMCNa	Hydrogel
8	Etoricoxib	HPMC	Hydrogel
9	Fluconazole	CMC	Emulgel, microemulsion-loaded hydrogel
10		HPMC	Hydrogel
11	Ketorolac tromethamine	HPMC	Hydrogel
12	Lidocaine	HPC	Hydrogel
13	Lidocaine hydrochloride		
14	Meloxicam	HPC	Hydrogel
15	Mepivacaine		Hydrogel
16	Piroxicam	HPMC	Emulgel
17		MC, HPMC, CMC	Microemulsion-loaded hydrogel
18	Propranolol hydrochloride	HPMC	Hydrogel

suitable for cutaneous application. Shahin et al. have experimented several jojoba oil-based emulgel formulations for the controlled delivery of the drug clotrimazole. In this formulation jojoba oil in lyophilic phase, Span 60 and Brij 35 as surfactants, propylene glycol as humectant and for its aesthetic benefits, hydroxypropyl methylcellulose, and/or Carbopol 934P were chosen as gelling agents. Here triethanolamine maintains the neutral pH range of 5.5–6.5. Thus it is clear that concentration and gelling agent significantly affect viscosity and the consistency of the examined systems as well as the release of drug [101] (Table 2).

Sabale et al. developed several hydrogels containing oil-in-water microemulsion, which composed of bifonazole (1%) and water. In this molecule oleic acid was used as oil, Tween 80/isopropyl alcohol as surfactant/co-surfactant mixture, and two grades of HPMC (K15 M and K100 M) in different concentrations of 1, 1.5, and 2% to improve the solubility and skin permeability of bifonazole. After several experiments, the formulation of microemulsion-loaded hydrogel is optimized based on viscosity and the polymer concentration. The constituents of this optimized microemulsion-loaded hydrogel were bifonazole (1%), oleic acid (6.25%), Tween 80/isopropyl alcohol (55%, 3:1), water (38.75%), and HPMC K100 M (2%).

A study which investigated the permeation on rat skin proves that bifonazole shows 80% permeability within 10 hours and sustained release of drug due to the presence of gelling agent. This can be described by the zero order model. Comparative with a marketed bifonazole cream, the developed preparation exhibited a good

stability over a period of 3 months with no skin irritancy and an antifungal activity [102].

Salerno et al. had done research on the in vitro release of fluconazole from different topical formulations, with the capacity to deliver the whole active compound and keep it within the skin. These are considered to be useful formulation, either for topical mycosis treatment or as adjuvant in a combined therapy for cutaneous leishmaniasis. Propylene glycol and diethylene glycol mono ethyl ether are used as solvent as well as enhancer, and sodium carboxymethyl cellulose is used as gelling agent in emulsions. Microemulsion-loaded hydrogel containing Transcutol P® has the ability to penetrate the pig skin and keep the drug within the skin and thus most effective in the aspect of antifungal affect. Further, the authors described that viscosity was not affecting the fluconazole release [103]. Among the studied hydrogels, those based on HPMC provide higher percentage of fluconazole release after 6 h, either in the presence or absence of glycerol (66.66 and 71.65%, respectively), where glycerol was the most effective release enhancer.

In several studies it is investigated the effect of structure and components of the vehicle on drug release and penetration by using nonsteroidal anti-inflammatory agents, such as diclofenac sodium, oxicams (piroxicam, meloxicam), and etoricoxib as model drugs [104–106]. For human cadaver skin, the highest flux value (2.43 ± 0.47 μg/cm^2/h), with a corresponding enhancement ratio of 27.5, is achieved with HPC-based hydrogel containing 5% menthol as penetration enhancer. According to the authors, meloxicam gel, consisting of 2.5% Klucel® gel, 0.3% meloxicam, 5% menthol, and the mixture of propylene glycol, ethanol, and water (1:1:1), can penetrate the skin effectively. Further four penetration enhancers (ethanol, propylene glycol, menthol, and azone) are added to meloxicam for better penetration to the skin from HPC-based hydrogels. The unique design of systematic formulation is also adopted for better result which has four factors. Among these, menthol influenced, in the greatest extent, the skin permeation of meloxicam sodium, followed by azone, ethanol, and propylene glycol respectively.

In addition research has been done to study the release of piroxicam based on an optimal gel base. On this account several gel bases consisting of different polymers in various concentrations like 3% MC, 2% CMC, 3% HPMC, 0.5% Carbopols 934 and 940, and 20% Pluronic F-127 are used to incorporate the piroxicam. According to the result, it is clear that 3% MC and 3% HPMC gel bases loaded with piroxicam microemulsion released the higher amounts of drug after 180 min (97% and 94%, respectively). These are also most suitable vehicle for topical delivery of piroxicam [107].

Thus drug release is controlled by the thermodynamic activity of drug, particle size, and diffusion through the preparation. It was suggested that diffusion of solute particles in a base as well as drug release decreases with increase in viscosity as the drug particles are trapped in high polymer macromolecules. So for the cellulose derivative-based hydrogels, it is considered that gel microviscosity controls the diffusion drug release.

Nowadays cellulose-based hydrogels are very important for the transdermal drug delivery as it is easy to apply and with no side effects. It can sustain and control the

drug release providing a better feeling for the skin compared with conventional ointments and patches. Numerous drugs such as hydrophilic, high molecular weight, and charged active substances cannot penetrate the skin for their structure and physical properties. For this case physical penetration enhancement techniques are adopting like iontophoresis, sonophoresis, electroporation, and laser irradiation. The hydrogels are very suitable for the formulation of drug by assisting the transdermal delivery by iontophoresis, sonophoresis, and electroporation. As hydrogels are high water content materials, they have some advantageous characteristics such as ease of loading into the device, suitability with the electrode design, good flexibility and fitting with the skin contour, strength, transparency, stability, and high electrical conductivity. Tavakoli et al. [108] investigated the transdermal iontophoretic delivery of celecoxib from several gel formulations, containing different gelling agents (sodium alginate, sodium carboxymethyl cellulose, hydroxypropyl methylcellulose, and Carbopol 934P). The hydrogel containing 4% HPMC K4M has the highest spreadability and ability to retain on the skin and released the highest percent of celecoxib after 5 h (41.5%) among other gels. Recently 2% HEC-based hydrogel are also used to deliver E-selectin antagonist CGP69669A by iontophoretic transdermal delivery. Nandy et al. have done a comparative study on efficacy of hydrogels on iontophoresis delivery of atenolol using hydrogel based on 3% sodium carboxymethyl cellulose or 3% methylcellulose, through excised abdominal rat skin. The results, obtained from the comparaitive study, indicated that cellulose derivative-based hydrogels were more suitable as solution for transdermal iontophoretic delivery systems, ensuring a sustained release of atenolol. Hence considering superiority of L-menthol as penetration enhancer compared to Tween 20, the NaCMC- and MC-based hydrogels, containing 1.5% atenolol and 2% L-menthol, were considered as the best drug delivery systems to achieve the desired drug level [109]. Other research works have reported the feasibility of using cellulose derivative-based hydrogels for the iontophoresis or electroporation transdermal delivery of diclofenac sodium and buprenorphine.

The ophthalmic drugs in hydrogels can increase the contact time with cornea, thereby increasing ocular bioavailability. A thermosensitive hydrogel composite is prepared by the incorporation of chitosan and b-glycerophosphate (GP). These hydrogels increase the transcorneal permeation by seven times compared to the normal aqueous solution, improving the ocular bioavailability, minimizing the need for frequent administration, and also decreasing the ocular side effects of ofloxacin. For ocular delivery of tombolo maleate, another type of hydrogels is prepared which contain chitosan and poly(N-isopropylacrylamide). Further Genta et al. modified these hydrogels, preparing bioadhesive chitosan microspheres for ophthalmic administration of acyclovir.

Cellular transport of large molecules across the mucosal surface can be improved by using chitosan hydrogels by opening tight junctions and thus useful for nasal absorption of drugs. Nazar et al. embed the N-trimethyl chitosan chloride into hydrogel matrix with PEG and GP for nasal drug delivery. These aqueous chitosan hydrogel combinations with medium or low molecular weight and a low degree of quaternization exhibit a sol-gel transition at within 7 min. For the nasal delivery of insulin, chitosan is also mixed with PVA matrix. Alsarra et al. reported that different

polymers like polyvinylpyrrolidone (PVP), chitosan, and carpool can be mixed with hydrogels for the nasal delivery of acyclovir. Among these polymers, the rate of release of acyclovir for PVA matrix is higher. In another study, quaternized chitosan and PEG with a small amount of abGP are incorporated into a thermosensitive hydrogel to be used for nasal drug delivery (60). After 4–5 h monitoring of these hydrogels, we can conclude that blood glucose concentration (40–50% of initial blood glucose concentration) is decreased.

Moreover for the drug delivery system, rectum provides the favorable environment of the drug activity. For local targeting of drug, this route is very much suitable and significant alternative to intravenous or other injection routes of drug administration. For monitoring the rectal activity, hydrogels containing hydroxypropyl methylcellulose (HPMC) and Carbopol 934 are widely used. The drug release and distribution of hydrogels in the distal portion of the large intestine is influenced by viscosity of rectal hydrogels.

4.3 Scaffolds for Regenerative Medicine

In the last decade, the use of cellulose and its derivatives as biomaterials for the design of tissue engineering scaffolds has received increasing attention, due to their unique biocompatibility, flexible methods of synthesis, range of constituents, and desirable physical characteristics. In the field of tissue engineering or regenerative medicines, scaffolds play very important role and developed to form a temporary, artificial, and extracellular matrix to support the cell attachment and the three-dimensional tissue formation [110, 111]. Therefore an ideal scaffold is a mimic of natural extracellular matrix. The very common method of tissue engineering includes the use of biodegradable scaffolds to support the growth and development of cells into tissues or by injecting the isolated single cell suspensions. In this field significant research work has been done to modify cellularized extracellular scaffolds to regenerate various tissues including bone, cartilage, heart, blood vessel, nerve, liver, and many other tissues [112]. Almost in all cases the scaffolds are very complicated in construction to meet the requirement of adequate cell-cell adhesion, cell-cell communication, and cell-extracellular matrix (ECM), which are all critically important tissue level functions. Thus it cannot allow cell migration. So for this high density cell seeding is applied inside bioreactors for static and dynamic cultures to establish adequate cell-extracellular matrix (ECM) and cell-cell interactions [113]. These seeded cells are very crucial into the scaffold for the regeneration of tissues to establish 3D cell culture. To overcome some of the drawbacks of conventional tissue engineering, alternative approach of cell sheet engineering was introduced which can eliminate the use of biodegradable scaffolds. Natural polymers are biocompatible, and thus by using it, we can avoid stimulation of chronic inflammation or immunological reactions and toxicity. These are the problems taking place with the synthetic polymer. Due to the high swelling capacity and biocompatibility, hydrogels have rubbery mechanical property. So they can incorporate cells (soft tissues) and bioactive molecules through the gelling process [114].

After degradation of cellulose, glucose is formed, which is a nutrient of cell. Thus they can serve as scaffolds that provide structural integrity to tissue constructions and control drug and protein delivery to tissues and cultures and, additionally, serve as adhesives or barriers between tissue and material surfaces. There are so many examples where cellulose derivatives are used for cell culturing including bone regeneration, hepatocyte culturing for an artificial liver, expansion of progenitor hematopoietic cells in culture [115], and suppression of matrix metalloprotease action in wound healing [116]. Poly(N-isopropylacrylamide) (PIPAAm)-coated tissue culture polystyrene (TCPS) dishes are prepared, avoiding the use of proteolytic enzymes with simple temperature variation. In some cases the thermosensitive hydrogels are used as a coating on TCPS dishes, for harvesting living cell sheets. These hydrogels are synthesized in the presence of aqueous methylcellulose, mixed with distinct salts on TCPS dishes at room temperature and subsequently gelled at 37 °C for cell culture. The 2% solution of methylcellulose (MC) with a viscosity of 4000cp is used to form gels at physiologically relevant temperatures. For the high viscosity of MC hydrogels, it is difficult to coat uniformly onto the tissue culture dish exhibiting subsequent unstable hydrogel system. For the cell sheet engineering this combination of MC hydrogels should be stable as the time of culture is increased. To overcome these difficulties in cell sheet engineering, MC hydrogels are modified by incorporating the collagen into the matrix which is suitable for the adipose tissue-derived stromal/stem cells (ASCs) and for the creation of multidimensional cell sheets [117]. Cellulose derivatives in the form of sponges or fabrics are used for the regeneration of cardiac, vascular, neural, cartilage, and bone tissues [118]. The cross-linking agent should be biocompatible as it is incorporated into the hydrogel network and might then be released upon degradation. The nontoxic hydrogels based on HEC, NaCMC, and hyaluronic acid are cross-linked with water-soluble carbodiimide and have an ability to cross-link with different polypeptides. The hyaluronic acid based hydrogel network provides the enzyme-sensitive site and is easy to control. Hydrogels are currently used for the minor tissue defects as they have nano-size mesh structure. Thus several manufacturing techniques of cellulose-based hydrogels are developed for enhancing the regenerative potential of cellulose-based hydrogels as well [119].

4.4 Wound Dressings

A wound, a defect, or a break in the skin can be a result of physical or thermal damage or, in the presence of an underlying medical or physiological condition, like diabetes and malignancies, persistent infections, poor primary treatment, and other factors [120]. The effective dressing can be described on the basis of healing procedure, conditions of patients, and the side effects of the used materials on the wound [121]. The steps of wound healing are inflammation, autolytic debridement, granulation tissue formation, and reepithelialization. The moist environment is helpful for wound healing. Hydrogels are designed as to maintain the right moisture balance in the wound bed, by hydrating the wound surface and/or absorbing the

wound exudates. They are very promising for wound dressing as sheets or in amorphous form. They also provide nonadherent dressings which can be easily removed without any damage to the wound bed.

A large scale of hydrogel dressing are available in the form of amorphous gels, gel-impregnated gauzes, sheets, or plasters for different wounds like minor burns. For the treatment of superficial burns, gel-impregnated gauzes are very useful, and for cavity wounds amorphous gels are preferred [122, 123]. Cross-linked hydrogel films can be obtained in a single-step process through coalescing nanoparticles or in situ forming gels (e.g., based on sprayable formulations) [124]. In some cases specific antibacterial agents are incorporated in the cellulose-based hydrogels, in order to further protect the wound bed from undesired microbial contaminations. The most advanced hydrogel dressings include antimicrobial agents, such as iodine and silver ions, in their formulation [125]. Recently a series of bacterial cellulose are used vastly due to its purity and high water retention capacity, providing favorable condition for wound healing. Most commonly used bacterial cellulose, Biofill®, was a partially dried BC membrane and was developed for wound healing of burns and chronic ulcers. It provides high performance in accelerating the healing process, pain relief, etc. [6] compared to other antibacterial cellulose derivatives.

The examples of commercially available cellulose-based hydrogels are Woundtab® (First Water) (sulfonated copolymer, CMC, glycerol, and water), Granugel® (ConvaTec) (pectin, CMC, and propylene glycol), and Aquacel® AgTM (ConvaTec) – which are made from NaCMC containing 1.2% silver in an ionic form. Modified carboxymethylcellulose (2.3%) and propylene glycol (20%) are also used in Intrasite Gel® (Smith & Nephew). The important challenge for the future is to establish the suitable wound care strategy for every patient, by offering the optimal products.

5 Conclusion

Thus cellulose-based hydrogels are having significant application in biomedicine and in pharmaceutical for their biocompatibility and environment-friendly property. Many research works have been done so far to enhance the property of cellulose-based hydrogels by modifying the structure to be used in diverse array of application in biomedical field. Currently cellulose-based hydrogels are modified by using nontoxic cross-linking agent into the matrix or cross-linking treatments, for further safety of both the final product and the manufacturing process.

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Cellulose-Based Hydrogels for Wound Healing

37

Isabel Orlando and Ipsita Roy

Contents

Abstract

Wound healing is a dynamic process involving several intra/extracellular mechanisms, which are triggered by cutaneous injuries. Wound repair consists of three separate but overlapping phases, i.e., inflammation, formation of new tissue, and remodeling. Although wound healing is an innate ability of every multicellular organism, specific precautions are required in some particular cases. One important aspect of wound management is maintaining a good level of moisture. It has been acknowledged by the medical community that an optimal level of hydration leads to increased healing rates, reduces pain, and improves cosmesis. In this context, it is essential to know the nature of the wound in order to choose the most suitable wound dressing. For instance, in the presence of a dry wound, where additional hydration is necessary, the use of highly hydrated hydrogels can allow the autolytic debridement of necrotic tissue when its surgical removal is not

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feasible. The ability to trap water up to thousand times their dry weight turns these materials into valid alternatives for wound healing applications. The use of cellulose-based hydrogels has become popular owing to their great degree of biocompatibility, low-cost, and biodegradability. Recently, different strategies have been investigated for the development of more efficient wound dressings, for instance, the introduction of antibacterial features using a combination of antibiotics and/or antibacterial polymers. Along with plant-derived cellulose, the use of bacterial cellulose membranes as wound dressings and skin substitutes is attracting considerable interest due to their innate hydrogel structure as well as their high chemical purity and mechanical properties. This chapter will present an overview of the most recent studies on cellulose-based hydrogels for wound healing applications, as well as the most recent outcomes of research in this field.

Keywords
Cellulose · Bacterial cellulose · Hydrogel · Wound healing · Dressing

1 Introduction

1.1 Wound Healing and Infection

A wound is defined as a skin damage that can occur as a result of a surgical incision, after contact with a penetrating body or due to an accident. Wounds can be classified on the basis of the number of skin layers involved as well as by the nature of the repair process. In the last case, they are distinguished between acute and chronic (Fig. 1). Acute wounds are generally caused by mechanical/chemical injures or burns and heal completely in the "right" time frame (8–12 weeks), while in the case of chronic wounds, no healing is usually seen within 12 weeks due to continuous exposure to the insult or physiological diseases such as diabetes or anemia [1].

As the injury takes place, different cellular mechanisms are activated in order to restore the damaged tissue. The process of wound healing involves specific but overlapping phases described as hemostasis, inflammation, migration, proliferation, and maturation (Fig. 2). Hemostasis, activated by bleeding, consists in the coagulation of exudates (in particular, clotting factors such as fibrinogen) and formation of a dry scab that strengthens the damaged tissue. Inflammation starts in the first 24 h and involves several mechanisms, including enzymatic degradation of necrotic tissue. Migration of keratinocytes and fibroblasts to the wound to regenerate the tissue under the clot occurs almost Simultaneously to the proliferation phase. During the proliferation phase, endothelial cells promote the formation of granulation tissue through angiogenesis and synthesis of collagen and extracellular matrix (ECM) components such as glycosaminoglycans and proteoglycans. The last stage of the process is the remodeling, which begins after 2–3 weeks from the injury and can last up to 2 years. During this period, the granulation tissue loses most of the endothelial cells, leaving a low cellular-density mass consisting of collagen and ECM proteins [3, 4].

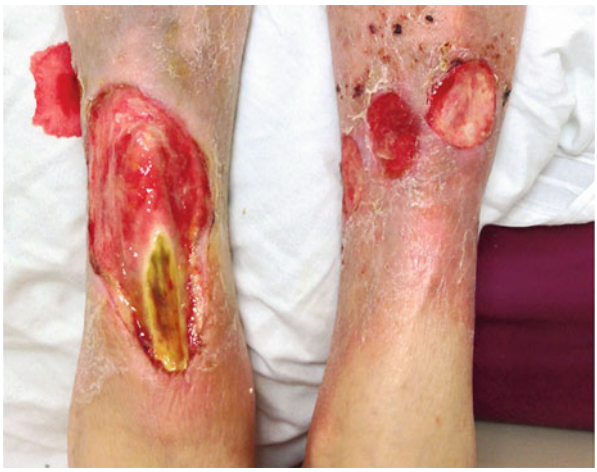

Fig. 1 Chronic wound [2]

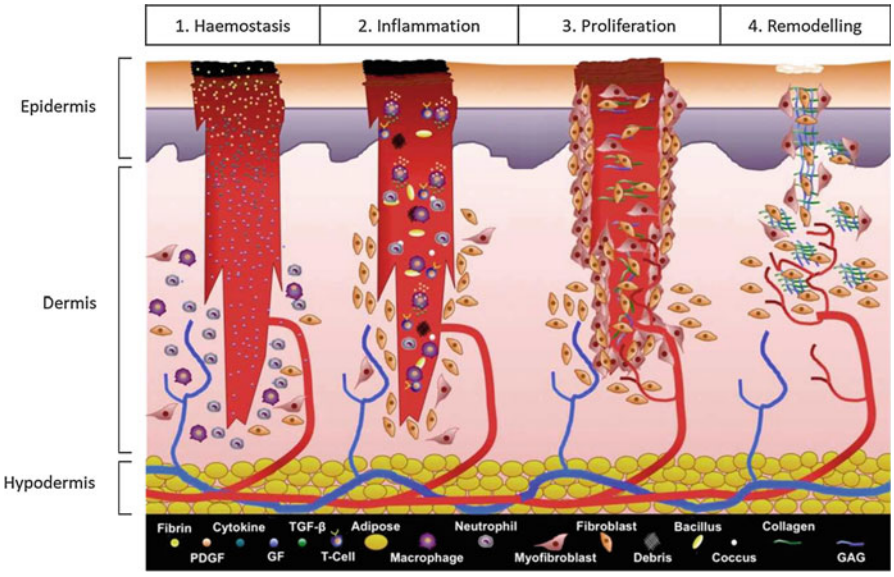

Fig. 2 Wound healing stages [5]

Many factors can influence the wound healing process, which can be classified as systemic, i.e., related to the health condition of the individual (for instance age, stress, physiological diseases), or local, meaning that they directly affect the wound. Among the local factors, one very important factor is the bacterial contamination of the wound [4].

Microorganisms can deposit and proliferate in the damaged area leading to the development of infections, hence resulting in prolonged hospitalization time, implant failure, and even morbidity [6]. The status of the infection can be determined

by Evaluation of the activity of the microorganisms. If the microorganisms are not proliferating, the wound is said to be contaminated, while if proliferation is occurring but no tissue damage is observed, the wound is defined as colonized. After these first stages, local infection/critical colonization occurs. At this level, inflammatory response should decontaminate the site; if not effective, the inflammatory phase can be prolonged. The last stage is spreading invasive infection, which is more likely to manifest in case of low immune system [4].

1.2 Wound Dressings

The choice of the most suitable wound dressing can only be addressed after evaluation of the wound. Wounds can be classified according to their appearance as necrotic, which are dark colored and dehydrated, covered by dead tissue; sloughy, which present a yellow/gray layer made of fibrin, leucocytes, exudates, and protein; granulating, which appear as pink or red due to their high degree of vascularization; and Epithelializing, i.e., wounds in the last stage of the healing process. A huge variety of wound dressings are available in the marketplace that can be chosen depending on the kind of wound as well as on its healing stage [7].

One of the most important aspects of wound managing is the level of moisture required by the wound. As studies conducted in the 1960s proved, maintaining an optimal level of hydration can result in many advantages such as increased healing rate, reduced pain, and improved cosmesis, for instance, by reducing the scar tissue. Again, the nature of the wound is crucial when selecting the most suitable wound dressing. In the presence of a highly exudating wound, a dressing able to absorb fluids is required in order to prevent maceration of the tissues. For this purpose, alginate dressings (that form a hydrophilic gel when in contact with exudates), foam dressings (made of polyurethane), and silicone and hydrofiber dressings (that help wound exudates wick through the textile fibers) can be used. When the wound has an already adequate level of moisture, a wound dressing able to maintain such conditions is applied. Examples are hydrocolloid dressings made of carboxymethyl cellulose, gelatin, and pectin, which form a moist gel with the wound exudates, and semipermeable film dressings, which are able to transmit moisture vapor without absorbing exudates. The third case concerns dry wounds that need additional hydration. When the surgical removal of dead tissues is not applicable due to low amount or particular health conditions, the autolytic debridement of necrosis can be achieved by application of hydrogels with high water content [7, 8].

Dressings can be further classified depending on their contact with the wound: primary dressings are directly applied to the wound, while secondary dressings are placed to cover the primary ones; island dressings, on the other hand, present a central absorbent area surrounded by an adhesive region. Moreover, they can be used as vehicles for the delivery of various drugs such as antimicrobial agents, growth factors or supplements depending on the particular needs of the wound [8].

1.3 Biopolymer-Based Hydrogels

In the last few decades, polymeric hydrogels have become the object of extensive research thanks to their unique features that make them suitable for a broad range of applications. An important role is played by hydrogels in the biomedical field, for instance, in the context of drug delivery, tissue engineering, and wound dressing [9]. Hydrogels are generally defined as highly hydrophilic three-dimensional polymeric networks. Due to their specific structure, hydrogels are able to swell without dissolving when immersed in a solution and to absorb and trap water molecules in their interstitial spaces in quantities up to thousand times their dry weight. Depending on the nature of the cross-linking between the polymeric chains, hydrogels can be classified as physical (also known as reversible hydrogels) or chemical (also called permanent). In the first case, the bonds can rely on physical entanglements, H-bonding, or hydrophobic/ionic interactions. The last example includes polyelectrolyte complexes (PECs), which consist of a combination of polyelectrolytes with opposite charges (i.e., calcium alginate and poly(L-lysine)). Chemical hydrogels, on the other hand, are based on covalently bonded networks obtained by the use of chemical cross-linkers such as ethylene glycol dimethacrylate (EGDMA) [10]. Thanks to their highly hydrated nature that can ensure a moist environment where applied, hydrogels are optimal candidates for the development of wound dressings to be used when additional hydration is required.

In this context, extensive research has been conducted on the use of biopolymers in the biomedical area. Biomaterials are defined as materials that are designed to be in contact with biological systems; applications of such materials include the replacement of tissues and organs and the development of scaffolds and drug delivery vehicles [11, 12]. In addition to this, all polymers produced by living organisms are defined as biopolymers. The synthesis of such biopolymers can have different purposes such as nutrient storage, catalysis of reactions, interspecies communication or communication with the environment, adhesion to other surfaces, conservation, and expression of genetic information. Moreover, polymers can be produced as structural components of the cell or the tissues [13]. Naturally derived polymers can offer several advantages over the synthetic ones and are attracting considerable interest for a wide number of applications. Thanks to their body tissue-mirroring nature, they generally show an excellent degree of biocompatibility. Examples of this are protein-based polymers such as collagen and gelatin and polysaccharides like cellulose and alginate. In most cases, their complex chemical structures and their unique mechanical properties cannot be achieved through synthetic pathways. In addition to this, they show a high degree of biodegradability by enzymatic treatment or after hydrolysis and have nontoxic degradation products [12, 13].

Being infection one of the main issues of concern for wound healing, a lot of effort has been made in order to develop antibacterial hydrogels for wound healing applications. To achieve this, a polymer possessing inherent antibacterial properties can be used as the starting material, or an external antibacterial agent can be loaded

into the polymeric matrix. Moreover, chemical or physical modifications can be carried out on the polymeric matrix, for instance, by introducing antibacterial functional groups or by coupling with an antimicrobial polymer. Many studies have been conducted on the use of hydrogels as carriers for metal ions (e.g., silver or gold), antibiotics, and other antimicrobial agents like antimicrobial peptides (AMPs). The release of the agents in the surrounding environment can be controlled by many parameters, e.g., pH or temperature. However, there are some limitations to the maximum concentration that can be loaded within the polymer network. To overcome this, polymers with inherent antibacterial properties can be used, for instance, by incorporation of chitosan or quaternary ammonium groups containing polymers [9, 14].

2 Cellulose-Based Hydrogels

Thanks to its great degree of biocompatibility, cellulose has been widely used for biomedical applications. Extensive research has been conducted on the development of cellulose-based hydrogels as novel wound dressings thanks to its great biocompatibility and biodegradability as well as availability. Several approaches have been investigated, involving chemical or physical modifications. In the study conducted by Basu et al., anionic nano-fibrillated cellulose (a-NFC) and cationic nano-fibrillated cellulose (c-NFC) were ionically cross-linked using calcium nitrate. a-NFC was obtained by TEMPO-mediated oxidation, while c-NFC was prepared by quaternization with 2,3-epoxypropyltrimethylammonium chloride (EPTMAC). a-NFC and c-NFC were then treated with Ca^{2+} in order to achieve the formation of two different hydrogels, i.e., a-NFC (only based on anionic NFC) and ac-NFC (containing both anionic and cationic NFC). These materials were then tested with respect to their biocompatibility using human dermal fibroblasts and monocyte-like cell lines; a level of viability higher than 70% for both types was observed. The inflammatory response of the hydrogels was also evaluated, demonstrating that a-NFC and ac-NFC present an inert behavior, not promoting inflammation, neither quenching an already occurring process [15]. A similar approach was developed in a study of 2015 focused on the production of anionic carboxymethyl and hydroxyethyl cellulose. A polyelectrolyte complex (PEC) was then developed using Al^{3+} as a cross-linking agent, resulting in the formation of a superabsorbent hydrogel. The sponge was characterized in order to assess its swelling ability. A dose-dependent absorption related to the Al^{3+} content was observed, probably due to an increase in the cross-linking density [16].

An optimized method for the purification of nano-fibrillated cellulose (NFC) from wood cellulose was described by Nordli et al. for the development of a dressing material. Cellulose pulp fibers were first subjected to repeated high-temperature treatment with NaOH, followed by TEMPO-mediated oxidation in the presence of NaClO. The fibers obtained were then homogenized using an Ultra-Turrax and tested in order to assess their degree of biocompatibility. The endotoxin level of the ultrapure NFC was evaluated, showing a value of 45 endotoxin units/g (EU/g),

while in previous studies, final values above the limit of 100 EU/g were observed. The cytotoxicity of the material was also determined using human fibroblasts and keratinocytes and a commercial carboxymethyl cellulose dressing as the control. No cytotoxic effect was detected on both fibroblasts and keratinocytes; however, a decrease in the metabolic activity (not associated with cell death) was observed, probably due to mechanical stress applied by the fibers. Cytokine production was also studied, and low stimulatory ability was observed for ultrapure NFC and the control [17].

An interesting article of 2016 investigated the use of NFC as carriers to deliver human adipose mesenchymal stem cells (hASC) into wounds in order to reduce inflammation and promote wound healing. NFC-based gel filaments were extruded by 3D-printing and cross-linked using glutaraldehyde to improve the wet strength. hASC were then seeded onto the scaffolds and showed good attachment even without coatings and confluency in 7 days. Cell attachment and viability were also evaluated after ex vivo suturing assay by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) test, and no significant difference compared to the control was observed [18]. 3D-printed structures were also obtained from two different nanocelluloses, i.e., TEMPO-oxidized and carboxymethylated/periodate (C-Periodate) oxidized nanocellulose. C-Periodate was found to be a suitable bioink for the Bioplotter, enabling to print self-standing 3D constructs characterized by a porous structure. Injection of $CaCl_2$ inside the 3D-printed scaffold caused the cross-linking of nanocellulose, resulting in the formation of a more compact structure [19].

Low-substituted hydroxypropyl cellulose (L-HPC) was also used to develop hydrogel sheets (HGS) and glycerol-impregnated hydrogels (G-HGS). G-HGS exhibited higher Young's modulus as well as increased tensile strength but same elongation ratio compared to the water-containing hydrogels. This was explained by enhanced intermolecular hydrogen bonding network between the L-HPC chains due to the presence of glycerol. Moreover, both hydrogels showed lower adhesive strength compared to the commercial silicone-based dressings as well as hydrogel dressings, turning these materials into optimal candidates for wound healing applications [20].

Hemicellulose-reinforced hydrogels were produced starting from TEMPO-oxidized NFC. Different types of hemicelluloses were extracted from different sources, namely, *O*-acetyl-galactoglucomannan (GGM), xyloglucan (XG), and xylan, and incorporated into the NFC-based hydrogels. Two sorption methods were investigated, i.e., pre-sorption and in situ sorption. Pre-sorption involved the adsorption of the hemicelluloses into the NFC network before the film preparation, followed by swelling of the films to achieve hydrogel formation, while in situ sorption consisted in the simultaneous swelling of the films with adsorption of the hemicelluloses from water. For both methods, a higher amount of hemicelluloses was incorporated within nanocellulose with high charge density due to its greater water uptake ability. The attachment and proliferation of fibroblasts on the hydrogels were also evaluated. Better results were observed for the scaffolds prepared by pre-sorption method using XG-containing low-charged NFC, probably due to the high mechanical strength given by the presence of XG [21]. Introduction of different

polymers and agents was also widely investigated to achieve a range of properties for several applications. An injectable hydrogel was developed using carboxymethyl cellulose (CMC) and pullulan for use as a postoperative anti-adhesive agent. CMC was cross-linked using tyramine in order to maintain its structural integrity during the in vivo experiments. Side chains of CMC were substituted with tyramine using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) and *N*-hydroxysuccinimide (NHS); phenol groups of tyramine were then used as cross-linking sites to perform an enzyme-mediated radical reaction. Pullulan was then incorporated to improve the adhesiveness properties of the hydrogel. The material displayed a high degree of biocompatibility compared to the positive control and low cell proliferation on its surface, which is a requirement for anti-adhesive materials to avoid formation of new tissue. Animal tests were also performed, and the use of CMC/pullulan hydrogel resulted in 27% abdominal adhesion formation, while the control group showed 100% adhesion [22].

CMC/silk sericin (CMC-SS) blends were prepared by Nayak and Kundu for use as biologically active wound dressing materials. Sericin is a protein with high hydrophilicity, which ensures a moist environment, and it has shown anti-tyrosinase and anticoagulant activity. Moreover, it is a waste product of the silk industry due to its weak mechanical properties; hence, it is widely available at low cost. A porous CMC-SS-based hydrogel was obtained by dual cross-linking using glutaraldehyde (for sericin) and $AlCl_3$ (for the carboxylic groups of CMC) in order to improve the mechanical properties of the scaffold. HaCaT cells, a keratinocyte cell line, were used to evaluate the biocompatibility of the material produced. Enhanced cell attachment and viability were observed in CMC-SS matrices compared to pure CMC; however, incorporation of sericin led to a decrease in the mechanical strength. A CMC/SS ratio of 1:1 was found to be optimal in terms of mechanical properties and biocompatibility [23]. A similar study of 2015 investigated the effect of the molecular weight of CMC on the properties of the CMC-SS hydrogel. Carboxymethyl cellulose with low, medium, and high molecular weight (respectively, L-CMC, M-CMC, and H-CMC) was used to produce a range of hydrogels with and without incorporation of sericin. A porous structure was achieved for all the hydrogels regardless of the CMC molecular weight, while smaller pore size was observed for the sericin-containing ones. Faster enzymatic degradation rates were observed for L-CMC- and M-CMC-based hydrogels, probably due to the higher number of glycosidic bonds, with consequent faster release rates of sericin. As a result, collagen formation from L929 cells was observed for these hydrogels thanks to the higher concentration of sericin available. Indirect cytotoxicity was also evaluated using L929 cells, showing no significant difference among all the hydrogels [24].

A very recent article described the development of a cellulose-based composite with high strength. In order to enhance the mechanical properties of the hydrogel, halloysite nanotubes (HNTs) were loaded into the matrix by continuous ultrasonication treatment and cross-linked using epichlorohydrin (EPH). HNTs containing hydrogels showed higher compressive modulus as well as higher resistance to deformation. The biocompatibility of the composites was evaluated using mouse

embryo osteoblast precursor cells (MC3T3-E1) and human breast adenocarcinoma cells (MCF-7). Increased cell viability was observed for all the composites compared to pure cellulose hydrogel except for the one with 1:2 weight ratio of cellulose and HNT, probably due to the excessive amount of halloysite nanotubes [25].

3 Bacterial Cellulose-Based Hydrogels

The last decades have witnessed increasing interest in the use of bacterial cellulose (BC) for biomedical applications. BC is externally secreted as nanofibers by several microorganisms such as *Gluconacetobacter* and *Agrobacterium* genera [26]. Its inherent hydrogel-like structure turns this polysaccharide into an ideal candidate for wound healing purposes, where a moist environment is necessary. This biopolymer is characterized by a highly crystalline structure, which results in excellent physical and mechanical properties such as higher tensile strength, Young's modulus, and water-retention ability. Moreover, since BC is produced with extremely high purity, It is inherently high biocompatible without the need of harsh purification processes [27]. In light of this, many studies have been conducted on this material for applications in several biomedical fields [28], with particular focus on its use in skin regeneration and wound healing [29, 30].

A study published by Lin et al. described the development of a BC-based scaffold with enhanced biocompatibility. A macroporous structure was achieved by physical punching to obtain uniform holes on the polymer surface and coated using a solution of alginate containing a range of extracellular matrices (ECMs), namely, collagen, elastin and hyaluronic acid, and several growth factors (i.e., B-FGF, H-EGF, and KGF). In order to improve the aggregation of the alginate gel layer, $CaCl_2$ was added. The release of collagen and hyaluronic acid as well as the diffusion of the growth factors was evaluated under physiological conditions, showing good release behavior and a gradual rate for all the components. The biocompatibility of the hydrogels was also evaluated using human fibroblasts (HS 68). Significantly higher cell viability was observed for the cells seeded onto the scaffolds containing collagen and H-EGF, while a decrease in the cell proliferation was registered when a higher concentration of $CaCl_2$ was used [31]. A similar approach was proposed in a recent work that compared the wound healing properties of a BC/collagen (BC/COL) hydrogel to a commercial collagenase-based ointment. BC pulp was prepared by trituration and mixed with collagen to form a gel. The in vivo experiment was performed on three groups to test, respectively, the BC/COL hydrogel (GI), the commercial collagenase ointment (GII), and the control (GIII). GI showed a faster reepithelialization and enhanced Adhesive properties compared to GII, especially in the first days of the healing process. On day 3, a moderate inflammatory reaction was observed in the group treated with BC/COL hydrogel, but on day 7 no significant difference was observed in the three groups. The higher efficiency in tissue repair exhibited by the BC/COL dressing could be ascribed to the biological properties of bacterial cellulose [32].

Thanks to the aforementioned biological properties of silk sericin (SS), some studies have been carried out on the use of this protein with BC to form composite films for wound healing applications. A recent article described the formation of SS-loaded cellulose membranes by impregnation using a solution of SS at different concentrations, i.e., 1%, 2%, and 3% w/v. The composites produced exhibited a smooth top layer of sericin and good integration between the two polymers, with increased matrix density without disruption of the fibrous structure of cellulose. The biocompatibility of the films was studied using NIH-3 T3 fibroblast cell line, showing no cytotoxic effect for all the samples. Moreover, enhanced cell viability was registered for the BC/SS hydrogels compared to the control with a dose-dependent trend related to the sericin content. Same results were obtained when the extracts were tested on keratinocytes. Similar cell attachment behavior was observed for all the samples and the control, but slower cell proliferation was shown for the cells seeded onto plain BC and BC/SS composites, probably due to the stiffness of cellulose [33].

In the study conducted by Awadhiya et al., BC was used to develop a composite together with agarose, a biodegradable polysaccharide with poor mechanical properties and excessive water uptake capacity. BC membrane were treated with a homogenizer to obtain a fine slurry and added to a solution of agarose and glycerol. The tensile strength of the films was evaluated, showing a maximum increase of 140% for the 20% w/w of BC composition compared to pure agarose. A higher amount of cellulose led to a decrease of the strength, probably due to low concentration of the agarose matrix, which caused the impossibility to hold and distribute the stress, or agglomeration of the cellulose fibers. For the same BC/agarose composition, a decrease in the water uptake values was observed, from 700% (pure agarose) to 450% at 37 °C and 350% at 4 °C because of the reduced mobility of the agarose chains at lower temperatures. This was explained by the presence of nonporous cellulose fibers, which could not absorb water, unlike BC membranes [34].

A composite based on BC and acrylic acid was produced by Mohamad et al. to develop a dressing for the treatment of burn wounds. The cross-linking between the two polymers was achieved by accelerated electron-beam (EB) irradiation at 35 kGy and 50 kGy to yield two hydrogels, namely, H_{35} and H_{50}. The biocompatibility of the materials was evaluated in vitro by indirect and direct contact method using mouse fibroblasts, showing cell viability higher than 85% at 24 and 48 h for both hydrogels. A lower amount of viable cells was found for the H_{50}, probably due to the higher number of -COOH groups in the AA, which could have lowered the pH of the environment. In vivo studies were also performed on burn wounds for the H_{35} due to its greater mechanical strength and higher water absorption and retention. No dermal irritation was observed up to 48 h after application of the hydrogel. Wound closure was also evaluated, showing no presence of scabs on day 7 for the H_{35}-treated group. Moreover, complete healing was detected on day 14 for the test and the control group, while the untreated group did not exhibit the same trend. A value of 60% was found for the wound closure in test group, which was higher than the positive control (40%) and the untreated group (30%). Histological studies highlighted enhanced epithelialization compared to the positive and negative control and higher

formation of keratin and hair follicles [35]. In a study published in 2016, the development of hydrogel microparticles based on BC and polyacrylamide was proposed for applications in burn treatment. Microfine BC powder was first dissolved and mixed with polyacrylamide, and the polymers were cross-linked using *N*,*N*′-methylenebisacrylamide (MBA). Microwave irradiation was then performed to achieve the formation of a hydrogel, which was micronized using a pulverizer and sieved to obtain microparticles with size in the range between 50 and 150 μm. In vitro cytotoxicity of the hydrogel was studied using mouse fibroblasts, showing cell viability higher than 85% at 24 and 48 h for both indirect and direct contact method. Significantly lower cell viability values were registered for the direct contact assay compared to the indirect, probably due to physical trauma caused by the weight of the microparticles. In vivo rat model was then used to further assess the biocompatibility degree. No skin irritation occurred after treatment with the hydrogel, and on day 7 no signs of scabs and hemorrhage were detected for the positive and the test group, unlike the negative control. Wound closure of 55% and 52% was achieved for the hydrogel-treated and the positive control, respectively, while for the negative control, a rate of 28% was recorded. Moreover, from the histopathological analysis, increased production of keratin, hair follicles, and blood vessels was detected for the test group compared to the positive control [36].

A very interesting strategy was proposed by Yu et al., where hollow BC microspheres were obtained via microfluidic process by culturing the bacteria in a hydrogel template. First, alginate hydrogel microparticles were produced by water-in-oil droplet technique using $CaCl_2$. To produce the core-shell structured particles, a two cross-channel junction with an outlet for the collection of the product was used. The alginate microparticles were dispersed in a bacterial culture medium and injected in the central channel, while a solution containing the agarose precursor and the bacterial culture (i.e., *Gluconacetobacter xylinus*) was injected in the first junction. To generate the droplets of agarose, the oil phase was injected in the second junction as the carrier fluid. The alginate-encapsulating agarose microspheres were obtained using a droplet nozzle of the same size as the alginate microparticles. The bacteria secreted the polymer only in the agarose section (shell) due to its lower density. Finally, the agarose was removed from the BC microspheres together with the biomass by high-temperature treatment, while the alginate was removed using sodium citrate. A 3D-scaffold was developed via self-assembly and seeded with human lung adenocarcinoma (PC-9) cells and primary epidermal keratinocytes. Bulk BC and solid BC microparticles were used as control. For both cell lines, a significant increase in the cell proliferation was observed for the hollow microparticles compared to the control. Wound healing properties of the scaffolds were also evaluated in vivo using a male Sprague Dawley rat skin model, showing enhanced cell regeneration and wound closure for the BC microparticles compared to the control and the bulk BC, probably due to the increased contact area [37]. A similar approach was proposed by Hirayama et al. to produce microstrand-shaped BC using a shell of calcium alginate hydrogel loaded with bacterial culture at different densities. NIH-3 T3 cells were seeded on the scaffolds, showing that confluence was reached in 72 h for the ones produced with greater initial bacterial density,

probably thanks to higher mechanical properties and porosity of the strands. Two different cellular constructs were then developed from the strands seeded with cells, i.e., coiled and barn-of-yard shaped. For both constructs, the initial shape was retained and the cells were alive and proliferating [38].

4 Antibacterial Hydrogels

A key section of the research on wound healing is focused on the development of antibacterial dressings. Extensive research has been carried out on the modification of cellulose and bacterial cellulose with the aim to introduce antibacterial functionalities or to load active agents. Many studies have been focused on the loading of antibacterial metals, especially in the form of nanoparticles. Mekkawy et al. described a green method for the reduction of silver nitrate by a fungal extract. The silver nanoparticles (AgNPs) thus obtained were then coated using different agents, namely, polyethylene glycol (PEG) 6000, sodium dodecyl sulfate (SDS) and β-cyclodextrin (β-CD), and incorporated into a range of polymers to achieve the formation of the correspondent antibacterial hydrogels. Among these, sodium carboxymethyl cellulose (Na-CMC) and hydroxypropylmethyl cellulose (HPMC) were used as gelling agents together with 20% w/w propylene glycol. The antibacterial properties of the products were evaluated by agar well diffusion assay, and the Na-CMC hydrogel exhibited higher bacterial growth inhibition. Moreover, it showed optimal viscosity values; therefore, it was selected for the in vivo experiment. The group treated with the AgNPs containing hydrogel showed faster wound healing and enhanced cosmesis compared to the control group treated with silver sulfadiazine. In addition to this, faster and higher bacterial growth inhibition was observed, with a presence of 2.7% of the bacterial count detected in the untreated group for the silver hydrogel and 30% for the silver sulfadiazine [39]. In a similar study of 2017, AgNPs were prepared in situ by reduction with a leaf extract in a solution containing bamboo cellulose nanocrystals (CNCs). Two different hydrogels were obtained using cellulose from two bamboo species, i.e., *Dendrocalamus hamiltonii* (DH-CNCs) and *Bambusa bambos* (BB-CNCs) and blended with Vaseline for topical application on diabetic mice wounded skin. On day 3, no signs of infection were detected in the Ag-hydrogel-treated group, while signs of pus were present in the untreated control group, and on day 10 faster wound healing was observed compared to the control. The inflammatory response was also evaluated, showing a reduced degree of inflammation compared to the control group, probably thanks to the presence of AgNPs that acted as protease inactivators [40].

Bacterial cellulose membranes were also loaded with Ag^{+} using $AgNO_3$ or silver zeoilites (AgZ) as silver sources. AgZ are microporous aluminosilicate minerals whose anionic cavities are filled with silver ions that can be released by cationic exchange, thus resulting in an antimicrobial effect. Two different samples were obtained, i.e., BC-$AgNO_3$ and BC-AgZ, by loading the silver source directly into the cellulose pellicles. Release studies highlighted a controlled and constant release

of silver ions from BC-AgZ over 96 h, while BC-$AgNO_3$ reached a plateau after 72 h. Moreover, a larger amount of silver was released by the zeolites-loaded BC. This result was further confirmed by the antibacterial studies performed against *Pseudomonas aeruginosa* and *Staphylococcus aureus*, which showed a higher bacterial growth inhibition for BC-$AgNO_3$ in the first 24 h, and a much lower activity at 48, 72, and 96 h, while BC-AgZ exhibited a greater long-term efficiency [41].

A very interesting study of 2015 described the development of a silver-containing dressing by loading a trackable fluorescent complex into sodium carboxymethyl cellulose (Na-CMC). The complex, $[Ag(ImD)_2]ClO_4$, was obtained by addition of $AgClO_4$ to a solution of dansyl imidazole (ImD) in dry acetonitrile. Na-CMC and polyethylene glycol were dissolved in a solvent, and the silver complex was added to form a homogenous solution. The slurry was then dried to remove the excess of solvent and layered between a sterile gauze and surgical tape. The release rate of silver ions was studied, showing a slow release in the first 8 h for the 1% of silver complex composition and, interestingly, a slow release in the first 3 h for the 0.5% of silver complex, followed by a linear release up to 24 h. This was explained by a quicker cationic exchange for lower concentrations of silver ions due to the lower resistance to the movement of external ions into the network. Antibacterial assays performed on *Escherichia coli* and *Staphylococcus aureus* exhibited promising results, with lower MIC values compared to other AgNP-based dressings [42].

The use of other metals has also been reported for the development of cellulose-based antibacterial wound dressings. One of the most common after silver is zinc, especially in the form of ZnO, due to its well-known bactericidal efficiency. A study published in 2017 described the impregnation of BC with ZnO nanoparticles (ZnO-NPs) in order to develop a wound dressing for application as burn treatment. ZnO-NPs were synthesized by reduction of zinc nitrate and loaded into the polymeric matrix by simple immersion in a dispersion of ZnO-NPs. The composites exhibited antibacterial activity against several strains, including *S. aureus* and *P. aeruginosa*, which have been reported as the prevalent microorganism species in burn wounds. A burn model was used to assess the wound healing properties of the films, showing similar results for the BC/ZnO-NP-treated group and the positive control (i.e., BC and silver sulfadiazine cream). Histological analysis revealed good epithelialization and tissue regeneration with smooth progression of healing for the positive control and the BC/ZnO-NPs group, while in the negative control formation of necrotic tissue and ulceration was observed as a sign of persistent inflammation [43]. Solution plasma process (SPP) was also used to produce ZnO in situ by reduction of Zn^{2+}. BC pellicles were saturated with zinc ions by immersion into solutions containing zinc nitrate and zinc acetate at different concentrations. The pellicles were then treated via SPP, which provided various active species such as atomic oxygen anion (O^-), super-oxide anion (O^{2-}), hydroperoxyl radical ($\bullet HO_2$), hydroxyl radical (OH•), and free electron (e^-) that act as strong reducing agents for the metal ions. Chemical characterization of the ZnO-NP-loaded pellicles showed similar results compared to the ones obtained via chemical reduction, confirming the

formation of the metal nanoparticles. The films were also tested with respect to their antibacterial properties, showing an increase in the bactericidal efficiency for the ones with higher concentrations of ZnO against both *S. aureus* and *E. coli* [44].

Along with metal ions, inherently antibacterial polymers can be incorporated in a hydrogel. Thanks to its great biological properties and wide availability, one of the most common polymers used for this purpose is chitosan. In the study by Fan et al., oxidized carboxymethyl cellulose (OCMC) was cross-linked to carboxymethyl chitosan (CMCS) to develop an antibacterial hydrogel. OCMC was obtained by oxidation of carboxymethyl cellulose using sodium periodate, while carboxymethylation of chitosan was performed in the presence of chloracetic acid. The modified polymers were then cross-linked by a reaction between the aldehyde of OCMC and the amino-groups of CMCS to form a hydrogel. Different concentrations of OCMC were added, and decreased gelation time was observed with greater amounts of OCMC due to the availability of higher number of cross-linking moieties. The wound healing properties of one of the hydrogels were evaluated in vivo using a rat model. For the group treated with the chitosan-carboxymethylcellulose hydrogel, no signs of infections were observed on day 3, while a scab was detected in some samples of the control group. The presence of a dry scab is believed to retard epithelialization, and an optimal level of moisture can help overcome this issue. On day 14, a significant difference in the wound size reduction was observed between the test and the control groups. Moreover, histological studies showed a smaller amount of inflammatory cells for the test group on day 14 compared to the control, and the degradation of the hydrogel did not lead to any adverse effects [45].

Several antimicrobial compounds have been loaded as leachable compounds into cellulose-based hydrogels. An interesting study published in 2016 reported the incorporation of galangin into a cellulose hydrogel by complexation with cyclosophoraose (Cys). Galangin is a flavonoid that has been proved to inhibit the activity of β-lactamase, resulting in intrinsic antibacterial activity also against a strain of methicillin-resistant *S. aureus*. Cys was chemically cross-linked with microcrystalline cellulose using epichlorohydrin in order to introduce complexation sites for the encapsulation of hydrophobic molecules such as flavonoids. Galangin was then loaded by immersion in a solution of 1 mg/mL for 2 days. In vitro cytotoxicity was studied by direct and indirect contact method using human dermal fibroblasts, showing no cytotoxic effects for the hydrogels developed, with results comparable to the positive control. Galangin release in PBS was analyzed using a UV-VIS spectrophotometer at 266 nm. A burst release was detected within the first 5 h for all the hydrogels, probably due to the dissolution of galangin from the surface. Higher release was observed for the cys-cellulose hydrogels compared to the control (i.e., cyclodextrin-cellulose hydrogel) probably due to the stronger interaction with cyclodextrin. The antibacterial activity of the hydrogels was then evaluated against *S. aureus* by incubation in the bacterial suspension followed by colony forming assay. The galangin loaded cys-cellulose hydrogel showed the highest antibacterial properties, with an efficiency of up to 99.99% over 72 h [46].

5 Conclusion

The chapter presents an overview of the state-of-art technology in the field of cellulose-based hydrogels for wound healing. Thanks to its great degree of biocompatibility, cellulose plays a central role in the biomedical area for an extensive range of applications. Moreover, it is widely available at low cost and can be produced from renewable sources, Making this polymer into one of the most used both for research and at industrial scale. Hydrogel wound dressings have been attracting tremendous interest in the last years due to their unique features and have become one of the main alternatives on the market for the treatment of dry wounds. In this context, an important part of the current research on wound healing is focused on the use of bacterial cellulose, thanks to its naturally obtained hydrogel-like structure. Moreover, the chemical structure of cellulose allows to achieve tunable properties based on the final applications. Bacterial infection represents one of the main current concerns in case of open wounds, especially due to the increasing resistance acquired by bacteria against the traditional pharmaceutical treatments. In light of this, extensive research has been oriented to the development of antibacterial wound dressings, either by loading the polymer matrix with leachable active agents or by permanent chemical functionalization of the substrate.

6 Future Perspective

A crucial aspect of the research on cellulose wound dressings is devoted to Address major problems related to the healing process. The use of hydrogels minimizes the pain related to the change of the dressing and ensures a moist environment that can facilitate the removal of necrotic tissue as well as the tissue regeneration. Additionally, in the context of skin regeneration, bacterial cellulose membranes represent an optimal material for the production of skin substitutes thanks to their innate structure and mechanical properties. However, a lot of effort needs to be put in the development of dressings with high biocompatibility that can promote the formation of new tissue, for instance, by incorporation of growth factors and extracellular matrix. From the bacterial contamination point of view, it is fundamental to design effective antibacterial dressings. A high efficiency in the bacterial growth inhibition and a long-term action need to be ensured, especially in the case of critically ill patients (i.e., diabetic or with low immune system). Future work has to focus on novel materials that are able to contrast the rising of antibiotic-resistant strains and the formation of biofilms, thus avoiding the need of surgery for their removal.

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Blended Gels of Sodium Carboxymethyl Cellulose Incorporating Antimicrobials for Absorbance and Wound Healing Applications

38

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Abstract

Wound healing is frequently enhanced by the application of dressings which maintain a moist environment and provide for absorption of exudates. In many cases, dressings with antibacterial properties are considered beneficial, while barrier properties and mechanical integrity are also important. This chapter initially reviews the role of natural and herbal antimicrobial products including propolis, honey, and *Punica granatum* (pomegranate) as potential constituents for wound care biohydrogels. The applicability of a wide variety of polysaccharides, including carboxymethyl celluloses, in wound care biomaterials is then considered. Sodium carboxymethyl cellulose (NaCMC) is able to form hydrogels by chemical crosslinking. Where a combination of properties is desired, blending with other polymers may be advantageous. The chapter concludes by examining recent progress with systems that incorporate a natural antimicrobial (propolis) within blended cryogels of NaCMC and poly (vinyl alcohol). PVA and its blends can form strong and relatively stiff hydrogels by a physical crosslinking process which occurs during freeze-thawing cycles. Crystallites are formed which anchor the polymer chains, creating a polymer network that can swell in the presence of fluids or exudates. Such composite gels retain acceptable mechanical properties even when loaded with up to 30% propolis. Dressings containing 15% propolis or more were effective against *S. aureus* and also exhibited high fluid uptake. Hydrogels containing NaCMC therefore have significant potential to meet the requirements for an effective wound care dressing, particularly when blended with natural antimicrobials and embedded in robust hydrogel matrices such as those of PVA cryogels.

Keywords

PVA · Cryogels · Polysaccharides · Carboxymethyl cellulose · Hydrogels · Wound care

1 Introduction

Infection is viewed as a major problem in open wounds and is the cause of death of many people who have suffered burns or trauma. Traditional wound care treatments include cleansing and the application of ointments or bandages, but increased understanding of both biomaterials science and wound healing has led to significant advances in wound care technology in recent years. Hydrogels containing synthetic or natural antimicrobials are now considered an important class of materials in terms of providing successful treatment options.

Several natural products present antimicrobial properties and promote healing and can themselves be considered as an alternative topical wound care treatments. Honey, propolis, pomegranate, and many other natural products can be used to treat wounds. Some of these products retain water in their structure, which can also assist healing by moisturizing the site. However, it is often considered advantageous to present these substances to the wound site by means of a suitable dressing which can consistently moisturize the area and provide for controlled release.

Hydrogels of many forms have also been used for wound healing for decades, mainly due to their high propensity for fluid uptake and their associated ability to provide moisture to the wound site. Such gels are based on tridimensional networks of hydrophilic polymers and include gels based on poly (vinyl alcohol) (PVA), starch, and sodium carboxymethyl cellulose (NaCMC) [1–4]. The potential of NaCMC to be a component of gels that promote healing and release natural antimicrobials is a focus of this chapter.

CMC is a natural polymer which can be converted to NaCMC by a two-step reaction, where the CMC is first modified to be able to absorb water and then reacts with a sodium compound. NaCMC is a polysaccharide that is generally biocompatible and relatively cheap and can absorb high amounts of water or aqueous fluids. NaCMC is able to form hydrogels by chemical crosslinking or, where specific properties such as increased mechanical strength are desired, by blending with other polymers. PVA and its blends can form strong and relatively stiff hydrogels by a physical crosslinking process which occurs during freeze-thawing cycles, and its role as a robust matrix for composite wound care gels will be explored in this chapter. The origin of these robust properties is the PVA crystallites that are formed during freeze-thawing, which securely anchor the polymer chains in a three-dimensional network. It will be shown that NaCMC blended or composite gels can combine high fluid uptake capacity with the ability not only to provide moisture but also to deliver antimicrobials to the wound site. Gels based on NaCMC can be considered not only for wound care but also as carriers for therapeutic drugs.

The goal of this work is to review options and approaches for the development of suitable hydrogel platforms for wound care, based on the properties of NaCMC and PVA hydrogels and the incorporation of natural antimicrobials.

2 Wound Healing

Wounds involve a disruption of the continuity of the skin and can be caused by incision, trauma, burns, or an underlying medical reason. Acute wounds, such as those due to surgery or trauma, usually heal in approximately 4 weeks and follow the three stages of healing. However, full recovery of skin mechanical properties can take up to a year [5]. Chronic wounds are usually linked with a chronic disease, such as diabetes mellitus, ischemia, or venous stasis disease, which interferes with the healing process (e.g., venous leg ulcers, diabetic foot ulcers). These wounds take longer to heal, present an insufficient repair process, and can suffer reduced oxygen supply [5–7].

Wound healing is a complex mechanism, essentially consisting of four stages: coagulation, inflammation, proliferation, and maturation. Chronic wound healing can stall in the inflammation phase, during which neutrophils and then macrophages arrive at the wound site.

The proliferative phase itself is comprised of four stages: epithelization, angiogenesis, granulation (endothelial cell migration and capillary formation), and collagen deposition (in which endothelial cells and fibroblasts are the main participating

cells). The final stage of chronic wound healing is maturation, where the collagen deposition is more organized, with the collagen fibers being thicker and aligned with the original collagen fibers of the skin. The tensile strength of the de novo skin reaches its maximum, 80% of the tensile strength of the original skin, after 3 months [3].

For wound healing, the wound site has to initially be cleaned (ensuring an absence of necrotic tissue, foreign material, and sources of infection). In addition to cleansing, the development of dressings led to the observation that a moisturized environment also helps wound healing. In 1960, Wichterle and Lim reported the possibility of the permanent use of plastics in contact with living tissue and that a moist environment accelerated reepithelialization [8]. Progression to the proliferative stage of healing may be affected by the bacterial burden, the moisture balance at the wound site, or the presence of necrotic tissue [2009 Gist]. In order to address the latter effects, hydrogels may be favored for the application since they provide a moisturized environment and they help autolytic debridement [9].

Microorganisms such as bacteria and fungi can colonize the wound site, resulting in infection, which can delay the healing [10]. Infection not only delays the healing; according to Madaghiele and colleagues, "Wound infection, which further increases the local tissue damage, is a common complication, while systemic inflammatory and immunological responses might lead to a higher predisposition to life threatening sepsis and multi-organ failure" [11]. It is therefore desirable to impart suitable antimicrobial properties to wound dressing hydrogels by incorporating bactericidal substances.

3 Natural Products for Wound Care

Synthetic antibiotics such as methicillin have been used in order to control and inhibit wound infection. However many bacteria, such as *Staphylococcus aureus* (the most common cause of infection in wounds), are resistant to these antibiotics. Herbal products are gaining increasing consideration as an alternative to synthetic drugs as a means to control infection [12–14].

Complementary and alternative medicine and Ayurveda medicine use herbal substances for therapies. Natural products have been used in wound care since they contain antioxidants, antimicrobials, and anti-inflammatory substances. These substances present in natural products have the potential to kill microbials and so stimulate healing, reepithelialization, and collagen production [15].

3.1 Wood and Plant Extracts

Aloe vera is a succulent plant that has a composition based on anthracene hydroxyl derivatives (aloins A and B_2), chromone compounds, and aloe resins A, B_2, and C. *Aloe vera* presents anti-inflammatory, antibacterial, antifungal, and anti-arthritis

effects [15]. It stimulates wound healing by enhancing fibroblast growth, it increases the oxygen access and the blood supply to the wound, and it stimulates the collagen production and the wound tissue collagen strength [16].

Wood extracts can also be useful for wound care. According to Sachdeva and co-authors, who studied the extract of *Jatropha curcas* L. "The plant contains Organic acids, Cyclic triterpenes stigmasterol, Curcacycline A, Curcin, a lectin Phorbolesters Esterases, Sitosterol and its d-glucoside. The leaf and bark have been shown to contain glycosides, tannins, phytosterols, flavanoids and steroidal sapogenins." In addition, ointment containing the extract increased wound healing rates in rats [17].

Arnica montana is a native herb of Central Europe and Siberia. It is known to have helenalin and dihydro-helenalin ethers, as well as sesquiterpene lactones as active anti-inflammatory/pharmacological compounds [18, 19]. The application of *Arnica* in dog wounds acted not only as an anti-inflammatory but also as an analgesic [20]. It is suggested that *Arnica* stimulates the tissue's extracellular matrix synthesis [21].

The bark of *Carallia brachiata* is effective in wound treatment, where its bark presents proanthocyanidins (carallidin, mahuanin), which have free radical scavenging activity, and parahydroxybenzoic acid. The extracts of *Carallia brachiata* were found to be active in the healing of rat wounds [22].

Curcumin (1,7-bis-(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione) is produced by certain plants and can be considered a wound healing compound. Curcumin acts as an anti-inflammatory, anti-bactericidal, and antioxidant agent. In addition, curcumin stimulates tissue granulation and collagen deposition, enhancing the wound healing [23].

According to Nicolaus and collaborators, the main constituents of *Calendula officinalis*, also a plant extract, are "Pentacyclic triterpenes from the ψ-taraxastene, taraxastene, lupene, Δ12-oleanene and Δ12-ursene types." *Calendula* is an effective wound healing agent, although its specific mechanism of action is not well described [24].

The composition of *Lavandula aspic* L. is based on terpenes and terpenoids, where linalool, 1,8 cineole, and camphor are the main components. Lavender oils and extracts present bactericidal, anti-inflammatory, and antioxidant activities. Lavender ointment enhanced rats wound healing rates and protein synthesis [25]. In addition, phenolic acids, flavonoids, flavones, and flavonols were found in *Lavandula angustifolia* and *Urtica dioica L.* (a plant of the Urticaceae family, known to present flavonoids, carotenoids, sterols, and minerals) extracts, presenting high antibacterial activity against *Staphylococcus aureus* [26].

Punica granatum (pomegranate) is a small tree from the Mediterranean region. It presents phenolic compounds, flavonoids, tannins, and epicatechin. Since it presents several active compounds, pomegranate extracts are bactericidal, anti-inflammatory, and antifungal. Pomegranate extracts increase the collagen synthesis and the wound contraction in rat wounds, and it presents higher activity against *P. aeruginosa* than against *S. aureus* and *E. coli*. It also diminishes the inflammatory phase time and stimulates the formation of granulation tissue [27–29].

3.2 Bee Products

Honey and propolis are produced by *Apis mellifera* bees, with compositions that vary according to the geographical location of collection, the botanical origin, the climate (temperature, rainfall), the season, and local plant nutrition, among other factors [30–32]. There are approximately 320 types of honey [33]. Propolis can be bacteriostatic and honey fungistatic, and, in high concentration, propolis can be bactericidal and honey, fungicidal [34, 35].

Honey generally presents flavonoids and polyphenols, which can act as antioxidants. The main antimicrobial agent in honey is hydrogen peroxide. In contact with aqueous solutions, honey's enzyme glucose oxidase is activated, which oxidizes glucose, generating H_2O_2. In addition, honey presents bioactive components, such as the vitamins E – tocopherol and A – retinol, and cinnamic acid. Honey presents a moisturized environment and is a barrier to bacterial infection as well as having antimicrobial activity [33, 35].

McLoone and coworkers compiled several studies regarding the antimicrobial properties of honey for wound care [36]. Honey from South Gondar/Ethiopia, from Amazonas/Brazil, and from Slovenia and Tualang and honey from Malaysia all inhibited *E. coli* and *S. aureus*. Some of the mentioned honeys presented activity against other bacteria. For example, Brazilian honey was effective against the *Proteus vulgaris* and *Klebsiella* species; Slovenian honey was active against *P. aeruginosa* and Malayan honey against *Streptococcus pyogenes* and *P. aeruginosa*. Furthermore, the growth of *C. albicans* was inhibited by honey from Al-Baha, Saudi Arabia [36].

Many honeys present antimicrobial activity related to the presence of H_2O_2. However, Manuka honey is obtained from *Leptospermum scoparium* trees (New Zealand and Australia), and its activity is not related to hydrogen peroxide but rather to the presence of MGO (methylglyoxal) and leptosperin. Manuka honey can act synergistically with synthetic antibiotics, e.g., vancomycin. It can work against infections with increased antimicrobial resistance, and it has been shown to enhance wound healing rate [37, 38].

Propolis presents different compounds with up to 300 constituents potentially present, which vary depending on its origin and climate. Flavonoids and phenolic compounds are found in propolis, such as CAPE and cinnamic acid derivatives that would be responsible for the antioxidant, anti-inflammatory, anticancer, and antiviral activities [32, 40, 41]. Propolis from temperate climates presents high amounts of flavanones and flavones and low phenolic acids and esters, whereas propolis from tropical climates is rich in prenylated derivatives of p-coumaric acid and some isoflavonoids and phenolic compounds [42, 43].

Propolis compounds' mechanism of action against bacteria is to alter the membrane permeability of the cell, inhibit cell division, and inhibit the synthesis of some proteins [35, 49]. Propolis has antimicrobial activity against gram-positive bacteria, e.g., *Staphylococcus aureus* and *Staphylococcus epidermis*, but limited action against gram-negative bacteria and also against some fungi, e.g., *Candida albicans*

[32, 39, 44, 45]. Several other natural products can be used in wound care, but the ones presented provide a suitable overview for the purposes of the present work.

4 Polysaccharides

This section will review a range of polysaccharides in the context of their having potential for wound care biomaterials applications. Among the polysaccharides of interest is agar, which is obtained from seaweeds. It is a hydrophilic, gel-forming polysaccharide, which can allow substitution on the hydroxyl groups and where the type and amount of substitution depend on, for example, its origin and type of extraction [46]. Agar is composed by agarobiose (4-D-galactopyranosyl-3,6-anhydro-L-galactose), which was identified after the partial hydrolysis of agar, by 2-methyl 3,6-anhydro-L-galactose dimethylacetal, which was identified in methylated agar, and by 3,6-anhydro-L-galactose dimethylacetal, identified through the methanolysis of the agar [47, 48].

Alginate is an anionic linear polysaccharide obtained from marine algae. It is composed of (1–4)-α-L-guluronic acid blocks (GG blocks), (1–4)-β-D-mannuronic acid blocks (MM blocks), and mixed sequences MG. The amount of each type of block depends on the algae type, age, and method of extraction. The M/G ratio determines the solubility of alginate in water, as well as its mechanical properties. In addition, the GG blocks are the main blocks to interact with calcium ions, which allow the chains crosslinking [49, 50].

Glucan is a class of polysaccharides that present glucose as monomer, e.g., glycogen, cellulose, and dextran. Glucans can be found in the cell wall of plants and cereal seeds. Some can be produced by fungi, molds, and yeasts. Depending on the bonds among glucopyranose units, different compounds can be formed. There are homopolymers of D-glucose, but the conformation of α- and β-glucans occurs according to the condensation of the OH^- groups [51]. Dextran and cellulose will be detailed later on in the present work.

Carrageenan (sulfated galactans) is anionic polysaccharides extracted from red algae, where the D-galactose molecules are bonded in an alternated α-1,3 and β-1,4 pattern. According to Webber and collaborators, "They are classified as kappa (κ), iota (ι), and lambda (λ) according to their sulfate substitution pattern and 3,6-anhydrogalactose content." Carrageenan dissolved in water forms a viscous solution, and it can be used as an emulsifier, for example, in the food industry [52, 53].

Chitin, a linear polysaccharide composed of (1–4)-linked 2-acetamido-2-deoxy-β-D-glucopyranose units, can be extracted from organisms like mollusks, crustaceans, insects, fungus, and algae. Chitin is a biocompatible and biodegradable material [54]. Chitosan is a cationic polymer obtained from the deacetylation of the chitin, which presents interesting properties, like accelerating wound healing [55].

According to Del Valle, "Cyclodextrins are cyclic oligosaccharides consisting of six -cyclodextrin, seven -cyclodextrin, eight -cyclodextrin or more glucopyranose

units linked by -(1,4) bonds. They are also known as cycloamyloses, cyclomaltoses and Schardinger dextrins. They are produced as a result of intramolecular transglycosylation reaction from degradation of starch by cyclodextrin glucanotransferase (CGTase) enzyme" [56].

Dextran is a glucose-based polysaccharide produced by *Leuconostoc mesenteroides* bacteria, and it is composed of α-1,6-glucopyranosidic linkages. The bacteria convert sucrose to dextran through an enzyme, dextransucrase [57].

Among the several available gums, guar gum, xanthan gum, gellan gum, acacia gum, and sterculia gum are used in biomaterials and for drug delivery systems [58–60]. The guar gum, extracted from a leguminous plant *Cyamopsis tetragonoloba*, is mainly composed of galactomannan and low amounts of moisture, protein, and fiber [61]. Gellan gum, an anionic polysaccharide composed of tetrasaccharide repeat unit of (1–3)-β-D-glucose, (1–4)-β-D-glucuronic acid, (1–4)-β-D-glucose, and (1–4)-α-L-rhamnose as the backbone, is produced by *Sphingomonas elodea* bacteria [62]. Xanthan gum is an anionic polysaccharide (1, 4-linked β-D-glucose backbone with trisaccharide side chain), which is the product of *Xanthomonas campestris* (aerobic bacteria) fermentation of sugars. In addition, these authors add "Acacia gum (GA) is an exudate from of Acacia Senegal trees and is a complex acidic branched polysaccharide." The acacia gum is a heteropolysaccharide containing a polypeptide, and it would be mainly composed by arabinogalactan and arabinogalactan protein [63].

Sterculia gum is "the dried exudates obtained from the stem and branches of Sterculia tree" [64]. Its composition is mainly galacturonic acid, β-D-galactose, glucuronic acid, and L-rhamnose [59].

According to Alonso-Sande and colleagues, glucomannan "GM is a hydrocolloidal polysaccharide consisting in β-1,4 linked mannose and glucose residues" [65]. Pectin is a polysaccharide composed by D-galactopyranosyluronic acid units [66]. Pullulan is a neutral linear polysaccharide consisting of α–1, 6-linked maltotriose residues. It is produced by *Aureobasidium pullulans* fungal [67].

Starch consists of mainly of two polysaccharides, amylose (a linear chain with few branches) and amylopectin (a very branched chain), and intermediate materials. Starch properties vary according to the amounts of each component [68]. Amylose usually is composed of smaller chains than amylopectin [69].

Xylan is a heteropolysaccharide, very abundant in plant biomass. Its chemical composition depends on the botanic source, although it basically consists of a linear backbone of 1,4-linked D-xylopyranose residues [70, 71].

4.1 Cellulose

Plants' cell walls are composed of bundles of cellulose fibers, ensuring the structural integrity of the walls [72]. Cellulose, $C_6H_{10}O_5$, a chain of sugar molecules, is the most abundant natural polymer and polysaccharide. It is found in plants, usually in combination with lignin and other polysaccharides. Cellulose is a linear homopolymer composed of D-anhydroglucopyranose units, linked by β-(1 → 4) glycosidic bonds. Cellulose, which is insoluble in water, is used in several applications, such as

in wood for construction, as textile fibers in cotton or paper, and as a raw material for charcoal production [73–76].

Bacterial or microbial cellulose is a version of cellulose produced by bacteria, for example, the gram-negative bacteria *A. xylinum* which consumes the nutrient broth (the source of carbon) through biochemical reactions to synthesize linear β-1,4-glucan polymers, which are later secreted by the organisms. Outside the cells, the polymers form microfibrils and ultimately bundles of microfibrils. The morphology and chemical composition of these fibers mimic the collagen fibers, and they are categorized as bioartificial, since these scaffolds are not synthetic or from animal origin. Microbial cellulose is a promising nontoxic material for wound healing [77, 78].

Cellulose can be chemically modified by reacting it with an alkali and then by letting the carboxymethylation occur, resulting in an anionic linear polymer with a carboxyl substitution, known as carboxymethyl cellulose (CMC) [75, 79, 80]. Among the cellulose derivatives, cellulose acetates are soluble in acetone and other solvents, while methylcellulose, ethyl hydroxyethyl cellulose, and sodium carboxymethyl cellulose are soluble in water. Sodium carboxymethyl cellulose is obtained through the reaction of cellulose with alkali and monochloroacetic acid. It is a linear anionic water-soluble polymer and a vastly used polyelectrolyte in pharmaceutical industry [76, 81].

Hydroxypropyl cellulose (HPC), according to Ogawa and collaborators, is a "cellulose-derivative to which a hydroxypropyl group is introduced as the substitute of 2, 3, 6-OH group, is soluble in both water and organic solvents. The average substitution ratio of the hydroxypropyl group in typical HPC is 2.0–4.5 per glucose unit" [82]. Carboxymethyl celluloses and hydroxypropyl celluloses are biocompatible polymers [83]. Dialdehyde cellulose is the product of a regioselective oxidation of cellulose using periodate. It is biocompatible and biodegradable [84].

4.2 Hydrogels of Cellulose with Synthetic or Natural Products

Sodium carboxymethyl cellulose (NaCMC) hydrogels can be crosslinked by gamma radiation, although considerable degradation can occur. It has been observed that NaCMC samples present optimum swelling degree at pH ~7, with reduced levels of swelling at low and high pH. The swelling degree of samples increases with temperature. The NaCMC is nontoxic and biocompatible, and the gels can be considered suitable for biomedical applications [85]. Hydrogels based on carboxymethyl cellulose-methacrylate crosslinked by photopolymerization presented superior swelling capacity, diffusion of proteins, and enzymatic degradation, although with a low shear modulus. The gels supported cell adhesion and viability, thereby showing initial potential to be used as scaffolds [83].

4.2.1 Hydrogels of Cellulose and Synthetic Molecules

Carboxymethyl cellulose-poly (ethylene oxide) hydrogels presented ~660% media uptake; they also exhibited enzyme degradation and acceptable biocompatibility.

Smooth muscle cells could adhere and migrate through the gels surface and pores, where extracellular matrix was synthesized [86].

Lower substituted hydroxypropyl cellulose (hydroxypropyl substitution ratio of 0.1–0.5) hydrogel presents increased adhesive strength and tensile strength with the increase of polymer in the hydrogel but lower adhesive strength than the silicone dressings, reducing the risk of trauma to the neo-formed skin. The gels also presented superior water uptake and transpiration [82].

Dialdehyde cellulose hydrogel loaded with chloramphenicol were bactericidal (against *S. pneumoniae*, *S. aureus*, and *E. coli*) and presented higher fibroblast adhesion and proliferation than the bacterial cellulose-chloramphenicol samples. Both samples released 99% of the drug within 1 day [84].

CMC-poly(N-vinyl pyrrolidone)/PVP hydrogels showed increased swelling capacity with increases in the proportion of CMC in the gels, while the gel fraction decreased. The blends presented mechanical strength superior to that of pure CMC gels, as well as superior flexibility and water uptake. The blends are viewed as being potential alternative low-cost materials for dressings [87].

4.2.2 Hydrogels of Cellulose and Natural Macromolecules

Bacterial cellulose and acrylic acid (AA) hydrogel crosslinked by electron beam radiation were investigated with respect to wound care applications. The increase in AA and in radiation dose increased the gel's mechanical properties, but nonetheless the gel's swelling capacity in simulated wound fluid decreased. The gels were nontoxic to human skin fibroblasts [88].

Cellulose-pullulan hydrogels (pullulan is a starch produced by fungus to improve adhesiveness and degradation) were formed through an enzyme reaction of tyramine-immobilized CMC with horseradish peroxidase (HRP) and H_2O_2 for crosslinking, adding pullulan. Tyramine was introduced to the CMC carboxyl group, where increased HRP and H_2O_2 raised the elastic modulus of the gels (G′). The gels supported low cell proliferation, exhibited low cytotoxicity, and prevented tissue adhesion [89].

BC (bacterial cellulose)-chitosan hydrogels adsorbed higher amounts of *Candida rugosa* lipase than microcrystalline cellulose-chitosan beds, and the same pattern was observed for the catalytic activity of lipase. The lipase also presented higher thermal stability when crosslinked to BC-chitosan material [90].

Bacterial cellulose (BC) and collagen have been combined in a hydrogel for wound care. Collagen is a class of protein present in a fiber morphology which guarantees the integrity of the extracellular matrix. In the combined hydrogel, collagen decreases the BC crystallinity and thermal stability. BC/collagen hydrogels promoted faster reepithelialization than dextran hydrogels and in addition showed adhesion to the wound site and promoted autolytic debridement [91, 92].

4.2.3 Hydrogels of Cellulose Incorporating Natural Antimicrobials

Some cellulosic membranes incorporating propolis have been developed recently. Biocellulose membranes were prepared by Barud and collaborators [45], and the membranes were then immersed in propolis to obtain bactericide dressings. These

membranes were effective against *Staphylococcus* species and also were seen to promote a better tissue repair in the early periods of the healing in the in vivo tests.

Cellulose hydrogels, loaded with honey and then gamma irradiated, were tested as wound dressings in rats. Increasing the dose of radiation led to higher gel content and to lower swelling degree (the presence of high degree of crosslinking led to low network expansion). It was observed that increased amounts of honey in the samples led to lower gelation (honey acts as a plasticizer, which impedes the crosslinking) and high swelling. The gels were effective against *S. aureus* and *E. coli*. In addition, wound contraction in rats was accelerated in the presence of CMC-honey gels [93].

CMC dressings containing chestnut honey, crosslinked by gamma radiation, showed potential as dressings, since they supported granulation tissue growth, they were non-adherent, they increased the rate of wound contraction, and they were effective against *S. aureus* and *E. coli*. In addition, increased levels of honey in the gels led to higher swelling capacity and lower compressive strength [94].

5 PVA Hydrogels

5.1 Properties of PVA and PVA Gels

The synthesis of poly (vinyl alcohol) (PVA) consists of two steps: chain polymerization of vinyl acetate monomers, forming polyvinyl acetate, followed by hydrolysis of the polyvinyl acetate, to generate the poly (vinyl alcohol), usually exhibiting a large molecular weight distribution [95].

Since the polymerization does not achieve 100% conversion, the PVA is a copolymer of PVA and polyvinyl acetate, where the degree of hydrolysis represents the degree of conversion. PVA with a high degree of hydrolysis has low solubility in aqueous fluids, since high amounts of acetate groups impede the formation of hydrogen bonds of hydroxyl groups. The dissolution occurs in temperatures higher than 70 °C [96].

PVA is a classic synthetic polymer used to synthesize hydrogels for wound care, due in part to its well-established biocompatibility [97]. PVA exists as a semicrystalline polymer, presenting inter- or intramolecular bonds [95, 98]. Hydrogels of PVA are transparent and biodegradable, they swell in aqueous fluids, and their mechanical properties can be adjusted according to the crosslinking process [95, 99, 100]. These gels can be used as contact lenses, in artificial hearts, as drug delivery systems, as articular cartilage, in catheters, as burn dressings, and as temporary skin substitutes [99, 101].

PVA hydrogels can easily be prepared by first dissolving the polymer in water or aqueous fluids. When PVA is placed in water, water molecules occupy the space between amorphous chains, possibly disentangling or dissolving them. PVA's crystals can unfold layer by layer, leading on to full dissolution of the polymer [102]. PVA's glass transition temperature (Tg) is affected by the molecular weight distribution, since the presence of short chains acts as a plasticizer, diminishing the Tg value [103].

PVA can be chemically or physically crosslinked. Chemical crosslinking can be done by radiation or by the addition of a chemical crosslinker. The chemical crosslinker must be a bifunctional reagent in order to react with the chains, connecting them. Chemical crosslinkers for PVA include boric acid, phenyl boronic acid, dialdehydes, dicarboxylic acids, dianhydrides, acid chlorides, epichlorohydrin, citric acid, succinic acid, and tartaric acid [104, 105].

When the PVA is submitted to gamma radiation, polymeric radicals are formed –(CH_2-C˙HO)– and/or –(CH_2-CHO˙)– and these radicals interact with each other through combination and disproportionation to form inter- and intramolecular bonds [106, 107]. Radiation technique crosslinks the PVA by forming covalent bonds between the groups originally in the chains, and it also sterilizes the gels. In addition, there is a high gelatinization and a low formation of sub-products [106].

PVA hydrogels can be manufactured by casting, where the polymer solution is poured in a mold and the PVA is physically crosslinked. Physical crosslinking by cryogelation involves freezing an aqueous PVA solution, causing ice crystals to form, thereby pressing together polymer chains in the remaining ice-free regions. When the chains are close together, they can pack into crystallites which involve hydrogen bonds between chains. When thawed, the ice crystals melt, leaving macropores, and the phase that is rich in PVA prevents the structural collapse of the gel [98, 107–111]. The PVA crystallites act as physical crosslinking points between chains, resulting in a nondegradable 3D structure – a cryogel [112].

The mechanical properties of the cryogel depend on the rate and on the temperatures of freeze-thawing, in addition to the dependence on solution concentration and on the molecular weight of the polymer. For PVA hydrogels, freezing cycles as short as 1 h are sufficient to make insoluble gels with a high swelling capacity (required to keep a moisturized environment that improves healing), and, although long cycles resulted in higher mechanical strength, they also contributed to lower swelling capacity [111, 113, 114].

5.2 Blended and Composite PVA Gels

PVA has been blended to different polymers in order to obtain appropriate material for wound dressings. PVA, poly(*N*-vinylpyrrolidone) and glycerol were mixed, cast, and crosslinked by freeze-thawing and gamma radiation. The gels presented improved water uptake. Silver was also incorporated in the gels, and these were able to accelerate healing and presented antibacterial properties [115].

PVA and polyethylene glycol (PEG) were combined with $CaCl_2$ and crosslinked with gamma radiation. The gel's swelling capacity was adequate to stimulate wounds' granulation and reepithelialization, and they were nontoxic and a barrier to microbial penetration [116].

Hydrogel fibers composed of PVA and polyacrylic acid (PAA) presented pH-sensitive properties, with the presence of PAA leading to higher swelling rate [117]. PVA-PEG hydrogels blended and submitted to electron beam irradiation presented high healing rates compared to gauze [118].

Biphasic systems such as PVA-gelatin have also been produced, and triphasic systems like PVA-chitosan-gelatin, abbreviated as PCG, were successfully manufactured by gamma radiation. They presented higher tensile strength than the comparator PVA-gelatin hydrogel. PCG gels presented appropriate hemostatic effects, swelling capacity, and water evaporation rate [119]. PVA can be combined to polysaccharides, natural polymers that could improve the PVA gel properties for wound care applications.

5.3 PVA–Polysaccharide Gels

Several studies have investigated the properties of gels formed from blends of PVA with polysaccharides, frequently for biomedical applications such as tissue engineering or wound healing. PVA-agar gels were prepared by casting without any additional crosslinking process, for purposes that require biocompatibility. In the swelling evaluation, the presence of agar was found to help the gels to keep the water uptake in the network. Hydrogen bonds are formed between PVA and agar. The agar altered the transition temperature of the PVA gels, whereupon the PVA-agar gels presented slightly higher melting temperature than pure agar. The gels did not present high mechanical properties, and the gels containing agar were more elastic [47].

Blends of PVA and alginate, chemically crosslinked with sodium sulfate, presented stability at temperatures in the range of 50–80 °C, and they were effective in the application of immobilized naringinase [120]. A freeze-thawing physical crosslinking process was applied in a different study, and PVA-sodium alginate hydrogels loaded with ampicillin showed antibacterial properties as expected. The presence of alginate increased the gel's swelling capacity and protein adsorption, but it reduced the gels elasticity and gel fraction [121].

PVA-β-glucan hydrogels prepared by casting without crosslinking presented promising results for wound healing. The presence of glucan increased the gel's swelling rate and the gels' ductility, the glucan was released from the gels, and rat wounds healed in half of the time compared to rats treated with gauze [122].

Carrageenan blended with PVA and freeze-thawed showed improved cell adhesion and proliferation [123]. PVA-κ-Carrageenan gels γ-irradiated presented higher swelling capacity with the increase of Carrageenan in the gels [124]. PVA-κ-Carrageenan freeze-thawed gels loaded with *Lactobacillus bulgaricus* extract showed antimicrobial properties and high healing rate [125].

PVA was blended with chitin and then chemically (epichlorohydrin) and physically (freezing-thawing process) crosslinked. The gel containing 25% PVA/75% chitin showed compressive strength 20× higher than the chitin gels. In addition, PVA-chitin gels were considered to exhibit suitable biocompatibility for the intended use [126].

PVA and chitosan have also been blended in several studies. Following chemical crosslinking, it was observed that the water content in the gels, the vapor transmission, and the permeability to vitamin B_{12} and creatinine increase with the rise of

chitosan in the gels [127]. In a separate study, it was observed that the addition of chitosan to PVA (freeze-thawed samples) increased the cells attachment to the gels without sacrificing the physical properties [128].

PVA-β-cyclodextrin hydrogels chemically crosslinked with glutaraldehyde were investigated as drug delivery systems [129]. Poly (vinyl alcohol)/β-cyclodextrin freeze-thawed hydrogels presented porous morphology, and the pore diameters depend on the amount of β-cyclodextrin. DSC analysis revealed that there were interactions between PVA and β-cyclodextrin. Tests also indicated compatibility between blood and the blended hydrogel [130].

PVA-dextran freeze-thawed blends presented altered crystallinity due to the presence of dextran. Dextran broadened the crystal size distribution and led to lower thermal stability of the gels [131]. In addition, the presence of dextran in the PVA freeze-thawed gels was associated with lower gel fraction, lower maximum strength, reduced thermal stability and higher swelling ability, water vapor transmission rate, elasticity, porosity, and protein adsorption [132].

PVA-gum hydrogels have also been considered for wound dressing applications. Sterculia gum crosslinked to PVA increased the gel's swelling capacity [59]. PVA gels and gellan gum can be crosslinked with gamma radiation, and the presence of the gum not only increases water uptake of the gels but also their biocompatibility [58]. PVA-acacia gum hydrogels presented superior swelling properties and drug release capacity [133].

PVA and konjac glucomannan (KG) freeze-thawed hydrogels presented characteristics superior to PVA gels and to KG gels. Hydrogen bonds formed between PVA and KG and PVA-KG gels presented higher elastic properties, Young's modulus, and compressive strength than konjac glucomannan gels [134].

PVA blended with pectin hydrogels has also been investigated with respect to the wound healing field. Cast blends prepared without any additional crosslinking process presented reduced elastic and viscous modulus above the gels' Tg as the proportion of PVA in the gels increased [135]. Freeze-thawed PVA-pectin hydrogels displayed interaction between the two polymers, where the pectin decreased the gel's crystallinity, and it was possible to incorporate drugs in the gels [136].

PVA and pullulan cannot be successfully cast in combination, since they undergo phase separation and present phase interfaces that weaken the gel's mechanical properties. Chemical crosslinking is required to obtain gels with appropriate characteristics [137]. PVA and starch can be blended and films can be cast. The addition of starch diminishes the tensile strength of the PVA-starch films [138]. In a separate study on gels, PVA and starch were blended and submitted to radiation. The presence of starch increased the gel strength and decreased the swelling properties. In addition, amylose and amylopectin were mixed to PVA separately in order to evaluate their influence on the PVA gel properties, and amylose was found to be the main reactive component of starch [139].

A xylan-PVA hydrogel has also been developed for potential biomaterials applications. Maleic anhydride-xylan (MX) was blended with PVA. The presence of MX decreased the swelling capacity of the gels and increased their strength. The hydrogels were considered generally nontoxic [140].

5.4 PVA Hydrogels Containing with Natural Products

A common strategy for the development of wound care biomaterials is to use gels based on PVA, often invoking their cryogelation abilities, to act as a matrix for natural antimicrobials.

In one example, PVA-polyacrylamide films prepared by casting were able to incorporate pomegranate peel [141]. PVA gels prepared by freeze-thawing and loaded with pomegranate or *Arnica* presented physical interactions between PVA-*Arnica* and PVA-pomegranate; the natural products lowered the PVA sample's crystallinity and swelling degree; pomegranate samples released more phenols and flavonoids to phosphate buffer saline (PBS) solution than *Arnica*. On the other hand, PVA-*Arnica* samples presented superior mechanical properties to those of the PVA-pomegranate samples [142].

In another study, PVA-poly(*N*-vinylpyrrolidone)-*Aloe vera* hydrogels were prepared by combinations of freeze-thawing and/or gamma radiation. Increased *Aloe vera* in the gels led to lower gel strength and gel fraction and to higher swelling degrees. The hydrogels containing *Aloe vera* accelerated wound healing rates in rats [143].

PVA-*Aloe vera* films prepared by casting showed that the components do not interact, where *Aloe vera*'s active compounds (e.g., anthraquinones, saponins) remain unaltered by PVA. The gels containing the lower (5%) amount of *Aloe* presented the higher bactericidal (*E. coli*, *P. aeruginosa*) and fungicidal (*Aspergillus flavus*, *Aspergillus tubingensis*) effects, probably because interactions between active compounds, which happen in samples with more *Aloe*, are avoided and there is less physical impediment to the delivery of these compounds. *Aloe* release happens in steps, where there is a burst release in the beginning due to the aggregates of *Aloe* on the sample surface, followed by a slower release, since the remaining *Aloe* is trapped in PVA networks [144].

Chitosan/PVA films loaded with pomegranate/mint extracts were prepared by casting for a potential food packaging application. The addition of extracts increased tensile strength. Samples containing the extracts presented antioxidant characteristics and were bactericidal to *S. aureus* and to *B. cereus* [145].

PVA-curcumin films were also prepared by casting. The samples sustained progressive curcumin release up to 17 days, and more curcumin was delivered to the media as the samples contained more curcumin in their composition. The release was more effective in acidic or basic pH than in neutral pH, since curcumin presents low solubility in water [146].

Targeting wound care applications, PVA gels incorporating a Brazilian propolis were produced by cryogelation. Samples delivered propolis to the media over 24 h and delivered more propolis to neutral media than to acidic media (Fig. 1). The presence of propolis diminished the crystallinity of the gels. More propolis in the gels meant more propolis delivery and a higher weight loss from the samples. Increases of propolis content up to 35% led to higher mechanical properties, while a 15% propolis content in the samples was enough for the gels to be active against *S. aureus*, Fig. 2. The material was also shown to act as a barrier to microbial penetration [147].

In an associated study, freeze-thawed PVA hydrogels incorporating a propolis of UK origin presented a swelling degree of at least ~200%, where the lower threshold

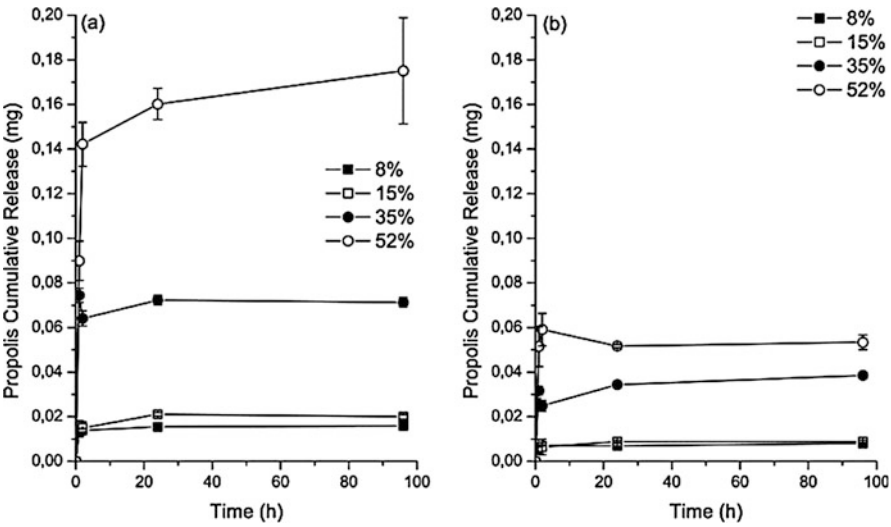

Fig. 1 Propolis cumulative release profile of PVA-propolis samples. The PVA-propolis samples were immersed in (**a**) PBS and (**b**) solution pH 4.0, and the propolis delivered was quantified after regular intervals of time for 4 days [147]

of swelling occurred for the samples with the highest amount of propolis. It can be hypothesized that the additional propolis may initially occupy and even swell the gels' pores, to then be replaced by media as it is released, leading to a lower apparent swelling effect. High amounts of propolis in the samples led to higher propolis delivery as expected [148].

PVA-honey films were prepared by casting and crosslinked with borax. The gels presented a swelling profile divided in two steps: first the filling of the network with media and, second, the release of honey and achievement of a swelling equilibrium. The gels permeability was appropriate for moderate or high exudative wounds. The gels were also active against *S. aureus* and were able to release erythromycin [149].

In another study, PVA-cassava starch blends were prepared by casting and mixed with nanoparticles of starch containing curcumin and then dried. The curcumin was released from the films by diffusion and erosion mechanisms. The films were non-cytotoxic to normal cells, but they presented an anti-cancer effect [150]. PVA-carboxymethylate chitosan-honey hydrogels crosslinked by gamma radiation and freeze-drying have also been studied. These gels were bacteriostatic and increased the rate of wound healing in rats [151].

5.5 PVA-Cellulose Hydrogels with Natural Products

This section considers work done to understand the properties of films and gels that combine PVA with various forms of cellulose, particularly as a matrix for natural antimicrobial products.

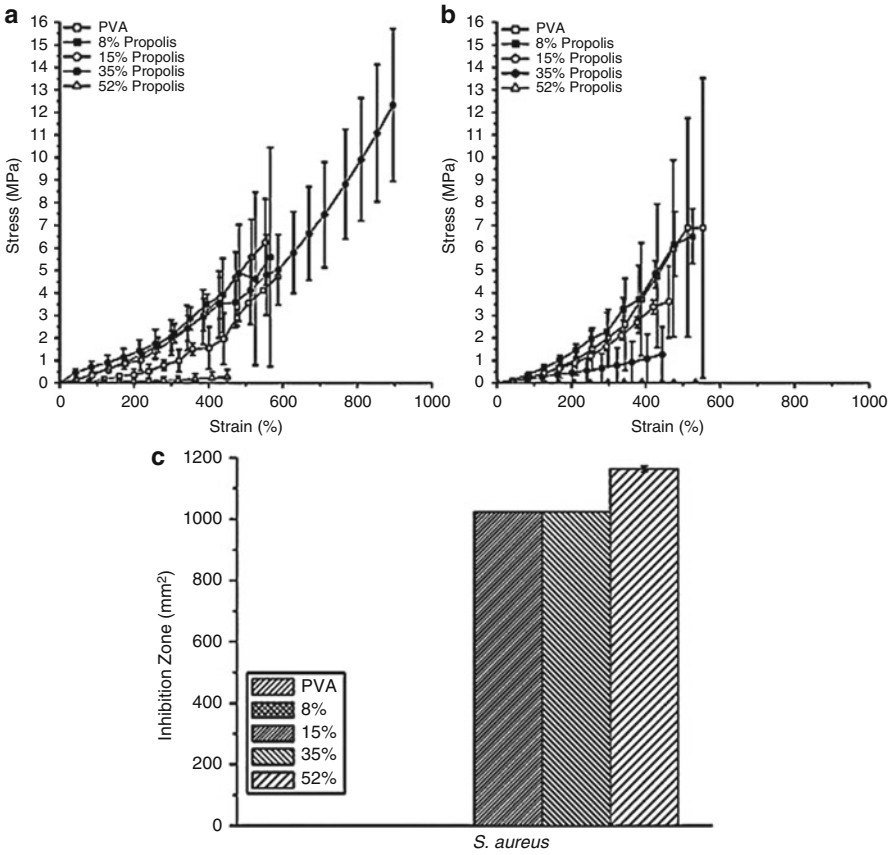

Fig. 2 Tensile tests of all swollen samples, PVA and PVA-propolis samples, after 1 day of immersion in (**a**) PBS and (**b**) solution pH 4.0; (**c**) antimicrobial activity of the PVA-propolis samples against *S. aureus* [147]

It has been observed that PVA covered the fibers of bacterial cellulose (BC) in cast dried composites of the two materials, filling the space between them, thereby increasing the density of the composite material. Incorporation of BC fibers increased the tensile strength and elastic modulus, but the toughness and the swelling capacity decreased [152].

PVA-CMC-gelatin were crosslinked with N,N′-methylene bis acrylamide, and the gels were loaded with povidone-iodine. The wound size of mice decreased considerably when treated with the gels containing iodine. Increasing the proportion of any polymer of the blend increased the gel's swelling capacity. The release of iodine increased with higher proportions of CMC or PVA [10].

PVA-bacterial cellulose multilayered blends were loaded with vanillin (4-hydroxy-3-methoxybenzaldehyde), an antimicrobial agent. The material's swelling behavior was altered by the presence of bacterial cellulose and vanillin, where

increases led to a diminished swelling degree of the gels. Bacterial cellulose could reduce the amount of available OH^- groups in PVA chains, lowering the PVA's polarity, crystallinity, and hydrophilicity. The vanillin release profile lasted 1 h [153].

In another study, freeze-thawed PVA-CMC hydrogels were combined with two synthetic antibiotics (ciprofloxacin and streptomycin) and two active anti-inflammatory natural products (tridax and the antibacterial turmeric). The gels loaded with ciprofloxacin and tridax presented high tensile strength and a water vapor transmission rate close to that of the skin. The gel containing tridax presented appropriate swelling capacity and gel fraction as well as displaying antibacterial properties against *S. aureus* and *E. coli* [154].

A separate study involved casting, mixing, and freeze-drying of PVA, CMC, and polyethylene oxide (PEO). In order to obtain membranes laden with either *Aloe vera* or curcumin, the respective component was mixed with the above polymers prior to freeze-drying. The gels presented high media uptake (~900%) and were able to release curcumin and *Aloe vera* to the media. The gels were bactericidal to the *S. aureus* and *E. coli* species. Increasing the *Aloe vera* or curcumin concentration in the dressings would be expected to increase their antimicrobial activity [155].

Cellulose/PVA/curcumin films were prepared by the ionic liquid method. There was compatibility between the phases, and the ionic liquid acted as a compatibilizer between PVA and cellulose. In addition, cellulose diminished the samples hydrophilicity [156]. Although electrospun materials are not in the scope of the present text, it is worth mentioning that ε-polycaprolactone-PVA-curcumin material for wound care was also studied. It was observed that 16% of curcumin was sufficient for the materials be active against *S. aureus* and *E. coli*, while maintaining fibroblast viability at 60% is considered to be an acceptable level [157].

In a recent study directed toward wound care applications, PVA-NaCMC hydrogels loaded with propolis were prepared by casting, followed by freeze-thawing. No chemical bonds between the three components were identified. The progressive incorporation of higher propolis amounts diminished the PVA gels' crystallinity and reduced the gel tensile modulus and strength (Fig. 3a). In addition, higher propolis content led to higher delivery of phenols and flavonoids (Fig. 3b), as well as high weight loss and swelling degree (Fig. 3c). 15% of propolis in the samples was enough to inhibit *S. aureus* bacteria (80% reduction) [158].

6 Conclusion

PVA is a biocompatible polymer and is a well-established hydrogel material. PVA blends have been produced by chemical (crosslinking agents, radiation) or physical (freeze-thawing) crosslinking. It is frequently combined with natural polymers or macromolecules, including polysaccharides and specifically CMC, when addressing wound care or tissue engineering requirements. Since the resultant blended or composite materials do not present antimicrobial properties, the addition of drugs or natural antimicrobials to these hydrogels is often contemplated. Synthetic drugs can cause resistance to some microorganisms, so herbal or natural products are

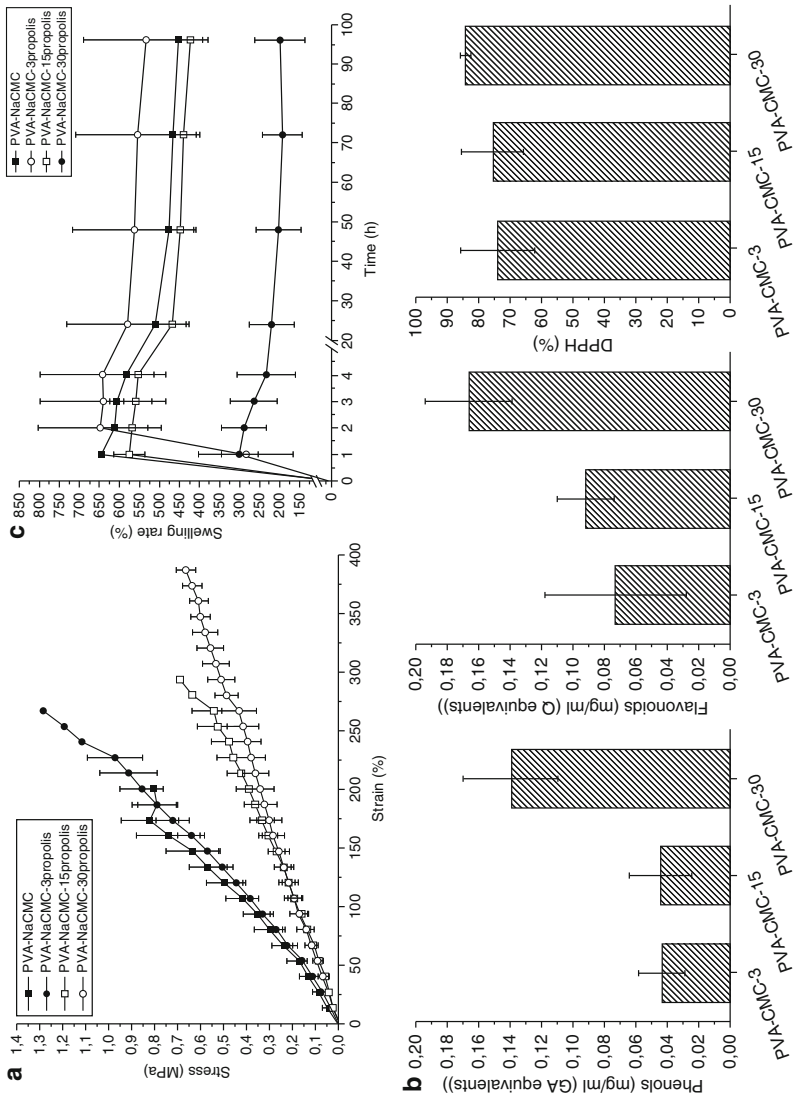

Fig. 3 (**a**) Tensile responses of the PVA/NaCMC gel samples containing 0%, 3%, 15%, and 30% propolis immersed in PBS at 37C for 4 days [158]. (b) Phenolic compounds and flavonoids delivery as well as DPPH scavenging activity of PVA/NaCMC gel samples containing 0%, 3%, 15%, and 30% propolis, where GA = gallic acid and Q = quercetin [158]. (c) Swelling rate of the PVA/NaCMC gel samples containing 0%, 3%, 15%, and 30% propolis immersed in PBS at 37C for 4 days [158]

attractive alternatives. In general, PVA-polysaccharide blends present high swelling capability combined with suitable biocompatibility. In combination with selected natural antimicrobial products, they can also have a bactericidal effect without compromising the wound healing process. Of the various polysaccharide options available, CMCs are widely available and can be successfully blended with PVA. In particular, blended gels of PVA and NaCMC, and releasing propolis, have been shown to have the ability to combine key attributes necessary for successful wound healing.

7 Future Scope

Hydrogels are a highly important class of biomaterial for the development of tissue engineering and wound healing therapies. Such applications require a strong understanding of the means by which the attractive characteristics of different kinds of gel components can be combined in a single product to meet the requirements of the patient. The overall objective of most hydrogel-based wound dressings is to maintain a moist and protected wound site, absorb any exudate, and deliver antimicrobial or therapeutic products to the wound site. Protecting the wound site requires a robust material, which is challenging for many hydrogel types.

In the work summarized here, the strengthening effect of the physical crosslinking in PVA-based cryogels has been exploited. There is much further scope to develop strong and highly elastic hydrogels based on other principles such as the double network gel approach or through fiber reinforcement. Strategies for improving the mechanical properties of biomedical gels could open up new avenues of material development and lead to interesting and more effective new solutions for patients by allowing greater flexibility to incorporate therapeutic potency.

Natural antimicrobials for wound dressings represent an attractive route for wound dressing development. The studies relayed in this chapter typically use extracts of natural substances which are incorporated prior to gelation of the biomaterial. It is possible that greater efficacy could be achieved through further study of the essential mechanisms of action at play and whether more sophisticated delivery systems could be developed in combination with future hydrogel structures. In particular, the possibility of developing nanoparticle carriers for natural antimicrobials would be worth exploring.

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Cellulose-Based Hydrogels as Biomaterials 39

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Contents

Abstract

Hydrogels are three-dimensional hydrophilic network structures that vary greatly in swelling/shrinkage properties against minor changes such as light density, solvent composition, ionic strength, pH, and temperature. Cellulose-based hydrogels are derived from natural sources which are biodegradable and

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low-immunologic. These hydrogels are produced in four different ways: those obtained directly from native cellulose (including bacterial cellulose), those derived from cellulose derivatives (methyl cellulose, carboxymethyl cellulose, hydroxy methyl cellulose, etc.), those obtained with other polymers as a composite, and finally those obtained from cellulose-inorganic hybrids. Cellulose hydrogels and its derivatives have many desirable properties such as high water retention capacity, high crystallinity, fine fiber network, easy formability, and high tensile strength. In addition, some cellulose derivatives exhibit intelligent behavior against physiological variables such as pH and ionic strength. Cellulose-based hydrogels have advantages such as better biocompatibility, less latent toxicity, and lower cost than the most synthetic polymer hydrogels. Because of these advantages, cellulose-based hydrogels are preferred to be used in industrial pharmaceutics and biomedical fields. This chapter will discuss applications of cellulose-based hydrogels in pharmaceutical industry and biomedical fields such as drug release systems, wound healing, and tissue engineering. In addition, future prospects on cellulose-based hydrogels will be addressed.

Keywords
Hydrogel · Cellulose · Biomaterial · Biomedical · Drug delivery · Wound healing · Tissue engineering

1 Introduction

In recent years, considerable advances have been made in the development of hydrogels, which are regarded as functional biomaterials, and these developments have expanded the design of versatile materials and minimally invasive treatments with the increase of processes and information in polymer chemistry [1]. Hydrogels are 3D polymeric networks whose major feature is the large water absorption capacity and are readily available in many biomedical applications [2]. Hydrogels, which have found applications in a wide range of biomedical and biotechnological fields, are dominantly used in drug release and tissue engineering treatments. Interest in the development of new materials, especially for hydrogel applications in biomedical field, is increasing day by day [3]. The global hydrocolloid market was reported as USD 5.43 billion in 2014 and is estimated to reach USD 7.56 billion by 2020 [4].

Cellulose is one of the most commonly found polymers in nature which can be obtained from a variety of sources such as marine animals, plants, and bacteria [5] consisting of anhydro-D-glucopyranose units linked by 1,4 linkages. Outstanding physicochemical properties and broad applications have received considerable interest in recent years by both scientists and industries. It is used in the biomedical field due to cost-efficiency, biocompatibility, and high mechanical and thermal stability. Despite these positive features, there is an important limitation, namely, low solubility that restricts its use. Modification procedures have been carried out in order to make the cellulose soluble and to gain beneficial properties such as antimicrobial

activity and mechanical strength. Chemical modifications include esterification, etherification, and oxidation, and the most common known derivatives thereof are hydroxyethyl cellulose, ethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, oxidized cellulose, cellulose acetate, and cellulose triacetate [6]. The adjustable characteristics of hydrogels containing cellulose and cellulose derivatives have promising characteristics due to its porous microstructure and good mechanical properties.

2 Drug Delivery Systems

The pharmaceutical industry develops, supplies, stores, and distributes new drug release formulations with the purpose of offering of safe, non-toxic, and cost-effective drug delivery systems. Hydrogels have begun to be of interest for drug release applications due to their highly porous structure, the ability to easily control the affinity of the hydrogels in swollen aqueous media, and the ability to adjust the density of cross-links in the gel matrix. The porosity of the hydrogels allows the drug to be loaded into the gel matrix and then leaves the drug along the gel layer depending on diffusion coefficient of the drug [7, 8]. Indeed, the benefits of hydrogels in drug delivery are dominantly based on their pharmacokinetics, which cause the drugs to form a depot formulation and maintain the presence of drug at a high local concentration in the surrounding tissues over time [9, 10]. Biodegradability or resorbability of hydrogels can be engineered by enzymatic, hydrolytic, or environmental (pH, Temperature, electric field, etc.) effects. In addition, some hydrogels with mucoadhesive and/or bioadhesive properties may be advantageous in keeping the application stationary or applying to non-horizontal surfaces [11]. Despite many advantageous characteristics, the amount and homogeneity of the drug loading into the hydrogel may be particularly limited for hydrophobic drugs [12]. The high water content and large pore size of many hydrogels usually result in relatively fast drug release in a period of several hours to several days [13, 14]. Each of these issues significantly limits the practical use of hydrogel-based drug delivery treatments in clinical use. A wide variety of cross-linking strategies including UV photopolymerization and chemical cross-linking techniques can be used for hydrogels prior to implantation. The main disadvantage of such approaches is the implantation of prefabricated material. Such problems can sometimes be achieved by making the preformed gel into micro- or nanoparticles [15, 16]. Hydrogels can also be gelled in situ (i.e., in vivo); however, these methods have also restrictions such as the potential risks with exposure to UV rays and the need for additional equipment or exposure to cross-linking chemical agents. The use of natural polymers in hydrogel synthesis is expected to effectively solve the source restrictions and environmental protection issues [17]. Hydrogels from natural polymers such as cellulose, starch, chitosan, and alginate are crucial because of their unique advantages including abundant sources, non-toxicity, biodegradability, and excellent biocompatibility [18]. Among them, cellulose which is the most abundant natural polymer found in

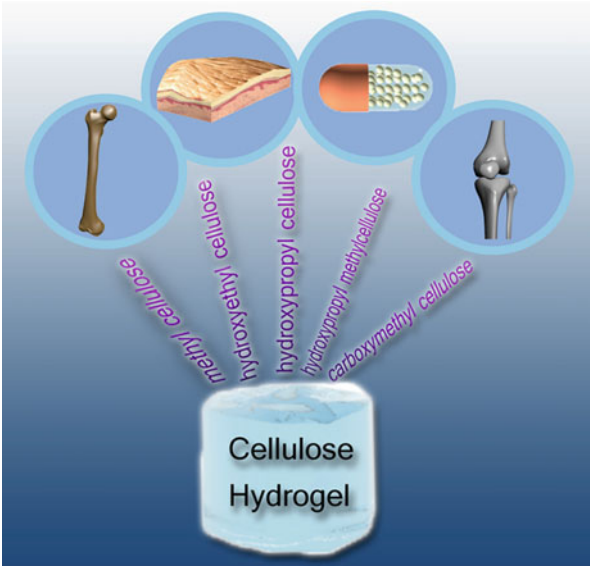

Fig. 1 Schematic presentation of the cellulose derivatives in biomedical fields

nature has attracted to interest in many pharmaceutical and medical applications including tissue engineering and drug delivery formulations (Fig. 1).

2.1 Cellulose Hydrogels in Drug Delivery Systems and Their Applications

Cellulose is insoluble in water and most of the organic solvents due to strong bonds between chains and intermolecular hydrogen bonding [19]. Powdered cellulose can be obtained by mechanical sizing techniques and used in medicaments as suspension agents, adsorbents, diluents, and thickening agents [20]. Microcrystalline cellulose (MCC) and oxycellulose consist of cellulose pulp without lignin and hemicellulose. Both powdered cellulose and MCC are used as bulking agents for active ingredient in oral solid dosage formulations. The MCC is a good bulking agent, binder, dispersant, and lubricant, which provides improved physical properties, and is also a suspending agent and stabilizer [21]. However, some of the properties such as loss of compressibility during wet granulation, low bulk density, sensitivity to lubricants, and medium viscosity limit the use in these applications [22].

Oxidized cellulose is chemically modified cellulose characterized by carboxyl groups instead of oxycellulose terminal alcohol groups. Woven cellulose dressing is not dissolved in aqueous solutions and acids but dissolved in dilute alkaline solutions [23]. Oxycellulose materials become transparent gel and swell in poor alkaline solutions. When it contacts with blood, a dark brown color forms a gelatinous mass, which becomes swollen and sticky [24]. For this reason, surgical interventions are recommended direct application to the leaking surface [25]. The oxidized cellulose forms dispersions in the water which are thixotropic (material that acts as a gel,

mixed viscous liquid when mixed) and can be used as film-forming materials in pharmaceutical applications. Moreover, controlled and sustained release formulations can be produced from oxidized cellulose [26].

Bacterial cellulose (BC) is a product resulted from functions of certain types of bacterium which has absolutely the same chemical structure of cellulose. The micro- and nanofibered nature of BC can improve the thermal and mechanical properties of the BC hydrogel material. The negative charge and the large surface area of the BC nanofibers are useful to control the loading of the drug on the composite surface [27, 28]. Moreover, the abundance of rich hydroxyl groups on BC fibers increases the chemical modification capacity with a range of chemical groups that can modulate drug loading and release from the material. However, the presence of highly crystalline regions and low absorption capacity limit applications [29–31]. Recent research studies suggest these limitations can be achieved by chemical modification of cellulose such as graft copolymerization with synthetic or natural polymers [32–34]. Biocompatible oral drug delivery systems with pH-sensitive characteristics composed of BC/acrylamide indicated a good drug vehicle for theophylline [34].

Nanocrystalline cellulose (NCC) is being investigated as a possible nanomaterial in targeted drug delivery due to its good physical properties for cellular uptake. Similar to other cellulose materials, the surface hydroxyl groups of the NCC also allow chemical modification to bind hydrophobic or non-ionized drugs with the NCC. Additionally, considering the biocompatibility of NCC on various mammalian cells, NCC can be a promising candidate as a carrier for targeted delivery of therapies [35].

The excellent biocompatibility of cellulose and its derivatives provides wide applications in pharmaceutical industry. Gelling agents which are commonly used in pharmaceutical compositions and industrialized topical hydrogel formulations such as ointments usually include cellulose derivatives such as methyl cellulose (MC), carboxymethyl cellulose (CMC), and hydroxypropylmethyl cellulose (HPMC) [36, 37]. Moreover, high availability in nature and non-toxic and cost-effective characteristics of cellulose derivatives make these materials advantageous in pharmaceutical industry [38]. According to the chemical modification of cellulose, the cellulose derivatives are divided into two main groups, namely, cellulose ethers and cellulose esters [38].

Cellulose esters are synthesized by hydroxyl esterification with various organic acids in the presence of a strong acid as catalyst. Cellulose esters are water-insoluble and have good film-forming properties which are useful for conventional coatings and controlled release systems in various applications such as pharmacy and semi-permeable membranes for agricultural and cosmetic applications [38]. The most important cellulose ester derivatives used in the pharmaceutical field are cellulose acetate, cellulose nitrate, cellulose acetate phthalate, hydroxypropylmethyl cellulose phthalate, and hydroxypropylmethyl cellulose acetate succinate.

Cellulose ethers which have good solubility, high chemical resistance, and non-toxic properties are used as stabilizers in the food and drug industry as well as in cosmetic formulations as the main ingredient [39]. They are synthesized by hydroxyl etherification with the appropriate alkyl halide cellulose. The basic examples of derivatives of cellulose ethers used in pharmaceutical applications are methyl cellulose (MC), ethyl cellulose (EC), benzyl cellulose, hydroxyethyl cellulose (HEC),

hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose (HPMC), hydroxyethylmethyl cellulose (HEMC), and carboxymethyl cellulose (CMC). Cellulose ethers are generally hydrophilic and are converted to hydrogels after exposure to water. After the coating material is removed with contacting water, the soluble hydrogels gradually dissolve in aqueous media, and thus, a dissolution-controlled drug release system is achieved. On the other hand, insoluble cellulose ester coatings remain a viscous gel around the tablets and provide diffusion-controlled drug release allowing drug molecules to diffuse within the layer [40].

2.1.1 Methyl Cellulose

MC is a cellulose derivative which presents as white, fibrous, odorless, tasteless, and slightly moisturizing powder or granules. It is found in a variety of pharmacopeias and different trade names including Benecel®, Methocel®, Metolose®, Tylose®, and so on [41]. MC has the ability to form thermo-reversible hydrogels when heated. It slowly swells and disperses in cold water [42]. When the pH value is lower than 3, acid-catalyzed hydrolysis of the glucose-glucose linkages occurs, and the viscosity of the methyl cellulose solutions decreases [41]. MC is not compatible with chlorocresol, mercuric chloride, phenol, resorcinol, tannic acid, silver nitrate, tetracaine, antimicrobial preservatives (cetylpyridinium chloride, methyl paraben, propyl paraben, and butyl paraben), mineral acid salts, and strong oxidizing agents [38].

2.1.2 Hydroxyethyl Cellulose

HEC is found as a whitish, tasteless, odorless, and moisture-attracting powder, and commercially available HECs can be found, namely, Cellosize HEC®, Natrosol®, Tylose H®, and so on [43]. It is readily soluble in hot or cold water and swells or partly dissolves in ethanol-water mixtures and polar solvents. However, HEC is virtually insoluble in acetone and many other organic solvents at pH 5.0–8.5 [41, 44]. Since aqueous formulations of HEC are sensitive to biological contamination, a water-soluble antimicrobial preservative should be added for long-term storage. Generally, HEC is considered to be a material that is predominantly non-toxic and non-contaminating for the dermal applications in pharmaceutical formulations [38].

2.1.3 Hydroxypropyl Cellulose

HPC is produced commercially with trade names of Klucel® and NISSO HPC® by Aqualon Hercules Inc. and Nippon Soda Co., Ltd. (NISSO), respectively [41]. It is soluble in water under 38 °C and is present in the market as a number of different viscosity types with molecular weight ranging from 50.000 to 1.250.000 Da depending on the degree of polymerization [38]. Similar to MC, HPC has also thermo-reversible characteristics [41, 45, 46]. Generally, HPC is considered to be a non-toxic and non-contaminating material and widely used as an excipient in oral and topical pharmaceutical formulations. It also does not show skin irritation or sensitization and included in the FDA Inactive Components Database (for oral solid dosage forms such as capsules and tablets, as well as for topical and transdermal preparations) [38].

2.1.4 Hydroxypropylmethyl Cellulose

In the current versions of pharmacopeia, it is called as Hypermellose. HPMC, designed for use in pharmaceutical applications, is produced under various trade names such as Benecel MHPC®, Methocel, Metolose®, Pharmacoat®, Tylopur®, and Tylose MO® [46–51]. The aqueous solutions of HPMC obtained at room temperature are converted into gels when heated to 50–90 °C and are completely thermo-reversible [34]. Heat resistance to gelation of HPMC is particularly influenced by various factors such as concentration in the medium and additives [38]. Thus, additives such as glycerol, sorbitol, and most of the electrolytes which cause coagulant activity reduce the gelling temperature, while the additives such as ethanol, Propylenglycol, and PEG400 led to solubilizing effect and raise the gel point of HPMC [52–56]. HPMC is considered to be a non-toxic and non-irritating excipient commonly used in topical pharmaceutical formulations and cosmetics and is also listed on the GRAS list [41].

2.1.5 Carboxymethyl Cellulose

CMC is used in the form of salts, namely, calcium CMC (CaCMC) and sodium CMC (NaCMC). NaCMC is usually used for pharmaceutical preparations, including hydrogels. Various commercial names including Akucell®, Aqualon CMC®, Aquasorb®, Blanose®, Tylose CB®, and Walocel C® are present [38]. In addition, the cross-linked CMC is water-insoluble biopolymer, and, in contrast to conventional NaCMC-based hydrogels, it is highly water-swellable to form superabsorbent hydrogels exhibiting superior mechanical properties and viscoelasticity [57]. Because of this feature, cross-linked CMC-based hydrogels have recently been investigated as potential wound dressing materials and dermal/transdermal drug delivery systems [57, 58]. Among the cellulose derivatives, only NaCMC is negatively charged polyelectrolyte (anionic) at pH values above the isoelectric point and is sensitive to pH and ionic strength [38].

Cellulose derivatives, particularly ethers, are used as adjuncts in the pharmaceutical industry for oral, topical (parenteral administration of the body), or parenteral (administration of drugs or serums by the routes such as intravenous as well as oral route) formulations [41, 59, 60]. The cellulose ethers contacting with water begin to swell, and the hydrogel layer grows around the tablets. The hydrogel represents a diffusion barrier for drug molecules that penetrate and release the polymer matrix. Resistance to acidic medium of the stomach makes these cellulose derivatives extremely useful as enteric coatings for tablets or capsules [41, 59, 61]. In addition, cellulose ethers such as MC, EC, HPC, and HPMC are essential constituents in formulations which aimed sustained drug release [62–64]. For example, HPMC is commonly applied as a compressed hydrophilic matrix, where hydration occurs following drug release through the combination of diffusion and dissolution processes of the matrix [40]. The literature suggests that tablets prepared by compressing drugs at certain ratios, hydrophilic adhesive hydrogels, and excipients (a substance suitable for the medicines to be prepared or a substance added to give a good taste) lead to prolonged release of the drug [7]. Analysis in simulated stomach and intestinal fluids under in vitro conditions showed that the drug is released

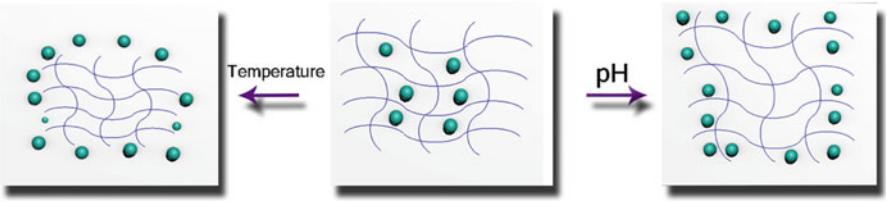

Fig. 2 Swelling and release behavior of active ingredient from hydrogel network structure

equally after the initial hydration phase [65, 66]. Furthermore, the studies on the release of some water-soluble drugs such as diazepam have been indicated near zero release [66]. The use of NaCMC as an excipient has been described as sustaining factor for drug release in solid oral dosage formulations [67]. In addition, the rate of drug release depends on the amount of water in the hydrogel, as well as on the parameters affecting the network (pore size and degree of cross-linking) [68]. Intelligent hydrogels are particularly useful for this purpose in the swelling-collapse transition which changes the network size of the hydrogel matrix associated with modifications of physiological variables (pH, ionic strength, and temperature) (Fig. 2) [68, 69].

Generally, controlled release behavior of oral medicines which pass from the stomach to intestine based on strong pH changes. In this context, cellulose-based polyelectrolyte hydrogels are suitable for this application [70]. For instance, CMC-based anionic hydrogels have been given promising results for colonic targeted drug release [71]. The most interesting feature of cellulose derivatives is that they can be injected without any change in their chemical, mechanical, and biological properties due to their thixotropic behavior [72]. HPMC hydrogels have been shown to carry and release both biomolecules and exogenous cells [73, 74]. Besides, due to the mucoadhesive properties, the residence periods of drugs in the nasal cavity can be extended significantly [75], and the high viscosity after hydration in the nasal cavity allows to maintain drug release [76]. Water-soluble cellulose derivatives such as HPMC, MC, HPC, EC, and CMC have been proven to be effective in increasing the intranasal absorption of drugs [77]. Thus, the use of cellulose derivatives may lead to increase intranasal absorption performance and bioavailability [78–80]. For example, apomorphine administered intramuscularly with CMC achieved a bioavailability of 102% relative to subcutaneous injection in rabbits [81] and a definitive bioavailability of up to 90.77% for ketorolac tromethamine administered with MCC [82]. It has been observed that the combination of cellulose derivatives with other absorption enhancers produces better efficacy than using these derivatives alone [83]. For example, intramuscular bioavailability of ciprofloxacin is low (18.2% and 19.46%) when MC and HEC are used alone in rabbits; however, it increased (22.35% and 25.39%, respectively) when combined with Tween 80 [84]. The effects on nasal absorption of HPC and azone addition provide a definite bioavailability of almost 100%, while it is only 25% for HPC use alone [79]. In Malik and his friends' work, beta-cyclodextrin (B-CD)-grafted CMC used as

a drug carrier for acyclovir against herpes simplex virus. Thus, the modification of CMC with β-CD has provided mechanical strength to hydrogel with an improved drug loading and release capability for the antiviral drug [85]. In another study, a new controlled drug release system was developed with CMC-grafted-polyacylamide/montmorilleonite hydrogel combined with iron oxide nanoparticles [86].

3 Wound Healing

The primary function of the skin which is the largest organ of the body is to act as a barrier against infections and excessive water loss. It is the most vulnerable organ of the human being and needs to heal to be able to continue functioning after injury. Repair mechanism of wounded area consists of dynamic processes involving inflammation, granulation tissue formation, reepithelization, and remodeling with an orchestration of a highly mixed process involving numerous cell types, growth factors, cytokines, and extracellular matrix (ECM) components [87, 88]. However, some injuries and diseases prevent these proceedings properly, and in such cases, external biomaterials which are called wound dressings are required. An ideal wound dressing should provide biocompatibility, effective absorption of exudates, creation of moist environment, high gas permeability, and formation of physical barrier against infection, proper physical and mechanical properties, cell attachment, proliferation, and differentiation [89–91]. Hydrogel wound dressing material is an ideal hydration environment, especially in burns because they are designed to hold moisture, absorb exudates, cleanse the wound, and create the ideal environment to promote the healing process [92, 93]. In addition to these features, transparency is another advantage for hydrogel wound dressings which allow monitoring of the wound healing [94].

3.1 Use of Cellulose Hydrogels in Wound Healing

Wound dressings containing cellulose have been extensively investigated due to their high water retention capacity [70, 95]. As an example, Gonzalez *et al.* developed polyvinyl alcohol (PVA)/cellulose nanowhisker composite hydrogels by the freezing-thawing technique. Hydrogels indicated promising results for wound healing due to their porous morphology, transparency, thermal stability, good mechanical properties, and water vapor transmission rate in addition to barrier characteristics against different microorganisms which can protect the wound against infection [96]. Another study investigated thermosensitive hydrogels composed of cellulose nanocrystals (CNC) and poly(N-isopropylacrylamide) (PNIPAAm), was synthesized by free-radical polymerization without a cross-linking agent. The PNIPAAm-CNC hybrid hydrogel with the highest CNC content showed the best mechanical properties. This hydrogel combined with metronidazole has been shown to have potential application as an injectable hydrogel for the infected wound healing applications [97]. Cellulose nano whiskers/poly(sodium acrylate)

films showed adsorption of proteins, were found to be biocompatible and antimicrobial, and had non-thrombogenic effect which are promising results for wound healing management [98].

Other cellulose-containing hydrogels in wound healing studies are BC and CMC hydrogels. Wound dressings produced with BC which is synthesized by some aerobic non-pathogenic bacteria differ from those obtained from plants [99]. High mechanical properties, crystallinity, and water retention capacity of BC have great potential for wound dressing development [100, 101]. Chloramphenicol (CAP)-loaded BC and 2,3 dialdehyde cellulose hydrogel (DABC) membranes showed effective resistance against *S. aureus*, *S. pneumoniae*, and *E. Coli* in addition to the increased adhesion and proliferation of fibroblast cells (L929) [102]. BC and acrylic acid (BC/AA) hydrogels produced by electron-beam radiation for the treatment of wound healing have been shown to be biocompatible and accelerate healing by increased neovascularization, reepithelization, and fibroblast proliferation compared to Intrasite Conformable® at the end of 14 days of *in vivo* study [103]. Moraes and colleagues compared a commercial collagenase ointment and BC/collagen (BC/COL) hydrogel. The poor adhesion of the collagenase to the wound bed has made it difficult to use. However, such difficulties were not encountered when BC/COL hydrogel is used. Moreover, macroscopic evaluation following in vivo study showed a better repair efficiency of the wounds treated with BC/COL compared to the collagenase ointment and control group without using any material [104]. Serafica *et al.* used BC with polyhexamethylase biguanide to heal ulcer patients. The hydrogel is designed to provide humidity by providing optimum conditions and prevent bacterial growth. Necrosis and hyper-granulation were drawn to normal levels and thus confirmed the healing process in ulcer wounds [105]. In addition to research studies, commercial BC products such as Bioprocess®, XCell®, and Biofill® are available on the market for topical applications. BC-based commercial products have been shown better performance than many other wound dressings with features such as absorption of exudate, reduction of wound pain, acceleration of reepithelization and healing, and reduction of wound infection and scar formation. BC-based wound dressings also present an ideal moisturizing environment and preserve an appropriate water balance by absorbing or releasing the fluid [99, 106, 107].

CMC has attracted interest in wound dressings due to its cost-efficiency, biodegradability, low toxicity, and the ability of exudate absorption. Nayak and colleagues developed a three-dimensional (3D) hydrogel matrix composed of CMC and sericin, which is a silk-coated protein, increased cell proliferation and binding of human keratinocytes (HaCaT) [108]. CMC hydrogels with chestnut honey as a bioactive substance indicated a high potential for use in diabetic mouse models with a significant reduction in wound area and increased tissue granulation [109]. Besides, combination of zinc oxide-impregnated mesoporous silica (ZnO-MCM-41) as tetracycline carrier incorporated with CMC hydrogel film increased proliferation of stem cells derived from adipose tissue in CMC/ZnO-MCM-41 [110]. There are also a number of CMC-based wound dressing products on the market (Table 1). Considering the current studies, it is expected that studies on the development of products based on cellulose derivatives which have potential as wound dressings are expected to gain acceleration.

Table 1 Commercial wound dressing products containing carboxymethyl cellulose

Trade name	Producer	Composition	Characteristics	Reference
Woundtab®	First water	Sulfated copolymer, CMC, glycerol, and water	A superabsorbent polymeric gel that can absorb and block the bacteria Useful for chronic injuries	[111]
Granugel®	ConvaTec	Pectin, CMC, and propylene glycol	A clear, viscous hydrogel provides a moist conditioning environment Useful in the treatment of partial and full thickness wounds	[112]
Aquacel®ag™	ConvaTec	Silver, NaCMC	Silver produces a bactericidal effect It absorbs the exudate and fills the gaps	[113]
Intrasite gel®	Smith & Nephew	Modified CMC and propylene glycol	Amorphous sterile gel used for flesh and deep wounds	[114]
Purilon gel®	Coloplast	NaCMC and water	Useful for necrotic wounds and first- and second-degree burns	[115]
Silvercel dressing®	Johnson & Johnson	Calcium alginate, CMC and silver	Medium to high exudate suction Useful for partial- and full-hip chronic wounds	[113]
Regranex®gel	Healthpoint biotherapeutics	Recombinant human platelet-derived growth factor BB (Rh PDGF-BB) and NaCMC	It stimulates the wound healing system and helps in the formation of granulation tissue. It encourages the proliferation of cells. It is easy to use	[116]

4 Tissue Engineering

The definition of "tissue engineering" officially introduced in 1988 at the National Science Foundation covers a recently complex area ranging from research in genetics and developmental biology to whole-organ engineering [117, 118]. Matrices which are generally called scaffolds are developed to support damaged tissue and promote differentiation and proliferation of cells in these matrices. As a result, damaged tissue is regenerated and replaced with the resulting matrix [119]. In

general, ceramics and synthetic and natural polymers are used in the production of tissue engineering scaffolds. These scaffold structures are expected to be biocompatible, be biodegradable, and have ideal mechanical properties and micro-/macrostructures [120]. To meet these requirements, hydrogel scaffolds have become increasingly attractive due to their ability to accommodate the polymeric structures, water absorbance, and compatibility with ECM [121].

The bone is a poorly vascularized tissue that provides a robust structural support, is resistant to load bearing, and must respond rapidly to metabolic demand [122]. Osteoblasts, osteocytes, lining cells, osteoclasts, and endothelial cells play roles in the formation of bone tissue [123]. Bone tissue can be damaged by various factors (degenerative diseases, cancer, etc.) and can heal spontaneously according to the extent of the damage, or regeneration is provided with various medical interventions such as autografts and allografts [118, 122, 124]. In the study of Fricaina *et al.*, regenerated cellulose was proposed to be suitable for femoral implantation, but it was found not to be suitable for osseointegration. The modification with phosphorylation overcomes this problem and led to cell attachment under in vitro conditions; however, no cellular mineralization was observed. After 6 months following femoral implantation to rabbits, histological observations, histomorphometry, and measurement of the amount of ^{45}Ca incorporated into the surrounding tissue revealed that phosphorus-modified cellulose showed better osteointegration than unmodified cellulose [125]. Sukul and colleagues observed that gelatin-nanofibrillar cellulose/β-TCP hydrogel scaffold construction containing 0.5 μM simvastatin supports cell differentiation under *in vitro* conditions and observed maximum bone formation in the mouse having 8 mm calvarial defect [126]. Fellah *et al.* also developed a self-cross-linking injectable hydrogel based on HPMC, which can treat critical-sized femoral defects. Composite hydrogel composed of silicon-modified HPMC (Si-HPMC) and biphasic calcium phosphate (BCP) ceramics was reported to support formation of granular cavities for bone growth. After 8 weeks of implantation in rabbit femoral injury, composite hydrogel was found to be mechanically more robust than trabecular bone [127]. On the other hand, after 4 years, J. Sohier *et al.* demonstrated Si-HPMC/BCP hydrogels are not yet suitable for bone tissue engineering. They have shown that the cells remained alive on the hydrogel but they were not proliferated and the remaining cells retain the osteoblastic differentiation [128]. Hydrogels composed of Si-HPMC and BCP ceramics could be used in the treatment of periodontal osseous defects. New bone formation was observed after 3 months following implantation to the dogs, and the BCP granules of the hydrogel material were observed to retain successfully during the healing process [129]. BC hydrogels promote adhesion, proliferation, and osteogenic and chondrogenic differentiation of mesenchymal stem cells [130]. Metabolic activities in osteoblast proliferation and extracellular mineralized matrix production were investigated in hybrid hydrogel scaffold constructs prepared from CMC-hydroxyapatite (HA). The chemical interaction between HA and CMC is predicted to occur between the carboxylate groups of the polymer and Ca^{2+} ions of HA [131]. Appropriate mechanical and cell proliferation was observed in the calcium phosphate (CaP)-CMC composite material prepared by periosteal inspiration at a rate of 10%

CaP, and increased bioactivity and CaP nucleation have been reported [132]. It has been demonstrated that the scaffold structure designed from TEMPO-oxidized BC and HA in the nanofiber construct is applicable for osteoblastic cell proliferation and differentiation, and TEMPO-oxidized BC hydrogel has been observed to enhance mechanical properties [133]. Injectable chitosan/glycerol phosphate (GP)/HEC hydrogel designed for bone tissue engineering applications does not show any angiogenic potential; however, the hydrogel with human bone marrow-derived mesenchymal stem cells along with chick chorioallantoic membrane has been showed angiogenic function for 3 days [134]. The hydrogel scaffolds prepared with quaternized cellulose and heparin by modification with adenine and thymine with cross-linking reaction using strong hydrogen bonds between adenine and thymine promised a future for bone tissue engineering applications with encapsulating osteoblast cells [135].

The injuries of the human articular cartilage are difficult to repair due to the avascular nature of the tissue [136]. Chondrocytes are responsible for the formation of cartilage tissue. Recent trends in cartilage engineering are based on the isolation of chondrocyte cells from the cartilage biopsy specimen and the injection to the damaged region with an ECM fluid by proliferating from the biopsy specimen [118]. Scaffolds designed for cartilage regeneration should be flexible which are capable of withstanding compression while providing a suitable environment for chondrocytes [137]. Hydrogel scaffold structures that mimic ECM in this regard have an extremely high potential. The CMC dialdehyde/gelatin/borate complex, designed to be injectable, biodegradable, and biocompatible with ECM, is important for tissue repair in cartilaginous defects with the intracranial migration of chondrocytes on the scaffold structure [138]. On the other hand, viscosupplementation, a therapeutic approach in the treatment of osteoarthritis, aims to treat the rheological properties of synovial fluid by mimicking it. Milcovich *et al.* have designed a new model hydrogel using a cationic modified HEC derivative. Both the mechanical properties and the matrix functions of designed hydrogel could mimic synovial fluid so that these properties are highly promising for use as viscosupplementation agent [139].

The BC has normally a pore size of ~0.02–10 μm which is smaller than the mammalian cell size, and therefore cells cannot penetrate the scaffold structure. To achieve this problem, the pore size of the BC scaffold modified with agarose microparticles (300–500 μm) was increased. The morphology of chondrocytes cultured for 14 days was found to be more prominent than that of pure BC [140]. In recent years, 15% BC content in the ear cartilage prosthesis was reported to meet the mechanical properties of the ear cartilage. Avila *et al.* performed *in vivo* and *in vitro* studies by increasing the content of BC to 17%. The increased BC ratio has proven to be a suitable biomaterial in terms of mechanical strength and low host-tissue response [141].

3D printing is a technology that introduces important innovations in health, engineering, and art. 3D printers are used in medical technology to produce patient-specific anatomic models for presurgical planning and to design specialized prostheses, medical devices, and drug delivery systems. Recent developments have

enabled 3D production of complex tissues using biocompatible materials, cells, and supporting components [142]. Kajsa Markstedt *et al.* designed biochemical human chondrocyte cells containing nanocellulose-alginate hydrogel with 3D bioprinting technology. *In vitro* cell culture studies have revealed that the nanocellulose-alginate hydrogel is a biocompatible and sustainable material for biochemical cell culture [143]. It has recently been observed that sea exopolysaccharide (GY725) stimulates chondrogenesis of adipose stromal cells under *in vitro* conditions. After 3 weeks following *in vivo* experiments with mice, it was observed that Si-HPMC/GY725 hydrogels produced high amounts of cartilage-like ECM containing glucose amino glycans and type 2 collagen [144]. Methacrylate-modified CMC hydrogel is also reported to be a promising candidate for the treatment of intervertebral dyskinesia degeneration due to the ability of successfully encapsulated "bovine nucleus pulposus" cells [145]. Physical cross-linking of polyvinyl alcohol and BC is recommended for cartilage repair due to various physical-mechanical properties [146].

Ideal eye bandage material should encourage wound healing and provide sustained release of pharmaceuticals. Regenerated cellulose-based hydrogels have potency in this field with high strength and light transmittance characteristics [147]. Optimal corneal prostheses must be mechanically strong and optically clean and have robust integration with surrounding ocular tissue, permeability to feeders, and surface epithelialization. A potentially new corneal prosthesis composed of bacterial cellulose and PVA has been explored with high water content, high visible light transmittance, appropriate UV absorbance, increased mechanical strength, and suitable thermal properties [148].

In addition to skeletal tissue engineering and ocular applications, cellulose-based hydrogels are also used in the fields of nerve regeneration, soft tissue augmentation, vascular graft, and cardiovascular tissue engineering. Post-endothelial cell development was observed on cocoon-like designed structures prepared with BC hydrogels and demonstrated use in "guided tissue regeneration" application [149]. Xu *et al.* produced a conductive composite hydrogel made from polyaniline (PANI) and cellulose for nerve regeneration. The cellulosic 3D network structure has served as a support for polyaniline with good electrical conductivity, soft physical properties, and excellent biocompatibility [150]. In another study, injectable redox-polymerized MC hydrogel material with selective enzymatic degradation properties was developed for soft tissue augmentation and reconstitution [151]. Artificial blood vessel is another focus area for cellulose hydrogels. BC hydrogel appears to be a promising biomaterial for artificial blood vessels. PVA addition into the BC showed significant improvements in mechanical properties and water permeability [152]. Photo-cross-linked fish elastin peptide/microfibril cellulose is suitable for varying tissue engineering applications because of elastic characteristics of composite hydrogel. Furthermore, the presence of elastin provides an advantage in a majority of mammalian tissues and degradability within the body [153]. Multilayered cellulose hydrogel tubes developed by inspiration from onion were found to be suitable for use as biomaterials with controllable layer thickness and structure, and the studies with L929 showed that the cells were easy to hold and multiply in layers [154]. It has been

discovered that the PVA-BC nanocomposite hydrogel exhibits similar mechanical properties to pig aorta and aortic heart valve [155]. Methacrylic anhydride-modified HPC hydrogel designed in 3D macroporous structure is found as a suitable material for adipose tissue engineering in the context of porosity (30–300 μm), swelling rate (12.94–35.83%), and storage modulus (0.75–4.28 kPa) [156]. Thermosensitive hydrogel nanoparticles synthesized from poly (N-isopropylacrylamide) (PNIPAM) and HPC led to less inflammatory and fibrotic responses compared with poly L-lactic acid and polystyrene nanoparticles on mouse model [157].

5 Other Applications of Cellulose Hydrogels

The production of cellulosic hydrogels is being explored extensively due to the fact that cellulose is both highly available in nature and biologically compatible [94] and is becoming attractive for *in vivo* studies in various applications [94, 158, 159]. Chemical cross-linking is an important method for increasing the mechanical properties of especially natural polymer-based hydrogels. However, some adverse outcomes may arise due to the toxic effects of the chemical cross-linking agents [1]. Nonetheless, researchers have extensively focused on non-toxic cross-linkers, different solvent systems, and polymerization methods. Chemical cross-linking, graft copolymerization, atom transfer radical polymerization, and other techniques have also been used to prepare cellulose-based hydrogels [160]. In addition to the chemical cross-linking methods, physical processes or blending with other natural or synthetic polymers has been developed [161]. Ogushi *et al.* performed a novel hydrogel prepared by cross-linking cellulose derivatives by enzymatic reaction under suitable conditions for mammalian cells. In this study, they developed a CMC containing phenolic fragments by conjugating the CMC with tyramines and concluded that CMC-Ph has a great potential for numerous applications including tissue engineering [3]. Cellulose hydrogel prepared with ionic liquids is found advantageous due to transparent, chemically stable, thermal-resistant, non-toxic, and easy recycling characteristics [162]. In the study of Aizad *et al.*, 3D scaffolds of CMC hydrogel containing *Centella asiatica* considered as one of the main herbs used in the treatment of skin problems and wound healing were studied. CMC scaffold was found to support the rapid growth of the hematopoietic cell line and protected the cells against physical stress. As a result, CMC could be considered as a chemical preventive agent for growth of the cancerous cell [163]. Photo-initiated cross-linking has been found to be the fastest and most effective way to solidify injectable formulations. In this context, Bayramoğlu et al.'s work includes a star-shaped methacrylated poly (propylene glycol-co-lactic acid) and methacrylated cellulose acetate butyrate resin hydrogels obtained by photo-polymerization method [164]. In the work of Zhu et al., CMC/polyacrylic acid (CMC/PAA) hydrogel developed by the reaction triggered by visible light was introduced. This method, which can be prepared in a simple manner, was predicted to be more applicable in hydrogel design and may open new potential

applications for biomaterials and tissue engineering [165]. The use of polyvinyl alcohol in hydrogels has very attractive properties for the biomedical field. However, polyvinyl alcohol having poor mechanical properties does not meet some tissue regeneration and repair requirements. For this reason, its use in combination with a polymer known to have good mechanical properties, such as cellulose, for the purpose of improving mechanical properties would be an ideal solution [166]. Porous hydrogels from HEC using citric acid as the cross-linker suggested having potential applications in the biomedical field [167]. Antibacterial activity is an important parameter of biomaterials to prevent postsurgical infections. The bactericidal effect of silver-containing biomaterials is known, and the interest in the development of these materials is increasing. Bactericidal effects of hemicellulosic hydrogels against *S. aureus* and *E. coli* may be used to prevent infection or treat infected wounds [168]. The following sections will provide information on the use in areas such as superabsorbent, biological imaging, etc., which are also intended for use in the field of health.

5.1 Superabsorbents

The World Health Organization takes attention to the fact that obesity is the reason of the second death threat after cigarette. Nevertheless, there are over 20 million overweight children under the age of 5; at the same time, more than a third of the adult population of the world is overweight, and almost 1 out of 10 people is obese [94]. Overweight and obesity treatment often involves a controlled diet with various physical exercises or, in more serious cases, surgical procedures involving specific drug treatments. Hydrogel is promising as an instrument for the removal of excess water from the body in the treatment of certain pathological conditions, such as renal failure and diuretic-resistant edema. In this context, the superabsorbent hydrogels allow controlling the swelling capacities by adjustment of the chemical composition and physical microstructures. Rapidly swelling super-acrylate-based hydrogels in aqueous solutions, as well as new cellulose-based hydrogels, have been shown to be suitable for the production of bulking agents in the diet stomach [94, 169]. Also for the treatment of diuretic-resistant edema, the use of hydrogels is naturally investigated to absorb water in the body [2]. Water will be absorbed by the hydrogel during the passage through the intestine; however, they do not swell in the acidic environment of the stomach (pH = 6–7). The hydrogel is then defecated, thus functioning without interfering with body functions [94].

Superabsorbents are also main constituent of disposable diapers. Commercially available superabsorbent hydrogels in disposable diapers have certain disadvantages such as poor mechanical strength, poor biocompatibility, and skin allergy risk. A novel cellulose-based hydrogel developed by simple chemical cross-linking of quaternized cellulose and natural cellulose in a NaOH/urea aqueous solution opened a new way to produce hydrogels with antimicrobial activity. Thus, these hydrogels showed potential for biomaterials used in hygienic applications [170].

5.2 Diabetics

As type 1 diabetes mellitus has increased globally, it is now becoming a major problem worldwide. There is sufficient evidence that insulin-dependent diabetes (type 1) is caused by autoimmune damage in the endocrine tissue that produces pancreatic insulin in both humans and animals. Insulin is administered to balance the blood sugar level of the diabetic patient, and glucose-sensitive hydrogels are developed to provide sensor-triggered insulin release. These developed hydrogels tend to swell or shrink according to their glucose concentration.

Thus, they play an important role in the treatment of diabetes by providing the appropriate dose of insulin for glucose concentration [171–173]. Membranes made of biopolymers such as chitosan, cellulose, and alginate have exhibited excellent "islet" compatibility due to their ability of desired diffusion properties for both insulin and glucose while maintaining integrity and functionality under *in vitro* conditions. For this reason, these biopolymers have been a potential candidate for future work in islet immunity isolation [174].

5.3 Aesthetics

In 1889, the first injectable implant, paraffin [175], was used, followed by liquid silicone in 1961, and the medical field further developed for aesthetic applications [176]. Since 1980, bovine collagen has been preferred in areas where wrinkles and scars are being treated [177]. In 1992, various other substances such as hyaluronic acid, known as dermal filler, were explored and begun to be used. Leonardis and colleagues conducted studies on the use of cross-linked CMC aimed to introduce long-term alternatives of hyaluronic acid and collagen for soft tissue augmentation and performed preclinical studies. The safety and side effects of the cross-linked CMC hydrogel after intradermal injections have been clinically evaluated, and it has been suggested as an ideal material for facial wrinkles [178].

5.4 Biological Imaging

The use of biological imaging plays an important role, as it is an essential technique for monitoring of disease and defects in the body. Computerized tomography scanning, one of the imaging modalities, has the potential to increase cancer risk for patients. Moreover, the X-ray imaging device, the most commonly used diagnostic medical imaging technique, is also a radiation source. For this reason, it is valuable to make materials with lower radiation for imaging. In the study of Wang et al., cellulose-phosphorus hybrid hydrogels were used for biological imaging and exhibited good pressure resistance and workability. In this work, for the first time, a new and safe cellulose-based hydrogel was developed using epichlorohydrin as a cross-linker in an alkali/urea aqueous system which offered to solve the solubility restriction of cellulose. The hydrogels were evaluated for their potential applications in biological imaging and were reported to be detectable both under the skin and in the stomach [179].

6 Conclusions

This chapter contains cellulosic hydrogels that are used commonly in the biomedical field as well as in pharmaceutical applications. Cellulose and cellulose derivatives do not have any side effects; they are easily injectable and release the drug from cross-linked gel matrix. Due to its purity and high water uptake capacity, BC and CMC have been extensively studied for wound healing applications, and a number wound dressing products have been marketed. Hydrogels prepared with different cellulose derivatives offer ease of use as support material for cells in tissue engineering applications. Nanocellulose, one of the most important cellulose derivatives of the last century, is at the forefront of tissue engineering applications in terms of outstanding mechanical and water absorption capacity. In conclusion, cellulose-based hydrogels are promising materials for drug release system, wound healing, and tissue engineering areas as well as other biological applications such as aesthetics, treatment of obesity, and imaging due to its high abundance, biocompatibility, and cost-effective properties.

7 Future Scopes

Cellulosic hydrogels, which may go directly to the target region, are likely to be involved in future studies. It is also possible that drug efflux can be controlled in terms of time and area. Another important feature of drug release systems is that hydrogel can be prevented from turning into a fluid liquid and can remain stable in the area to be applied. New alternatives to the modifications such as oxidation, methylation, propylation, carboxylation, etc. could be introduced to achieve the solubility problem of cellulose. Although the tight fiber structure of BC is restricted for cell attachment, it also promotes the adhesion and proliferation of chondrocytes by increasing the pore width in a composite hydrogel prepared with alginate. Future studies may focus on this restriction and could solve this problem with combination of other biopolymers with BC or changing the production process conditions. Moreover, nanocellulose-based hydrogels have attracted the scientific world since last decade. Promising results indicated that nanocellulose-based biomaterials will impact the future vision of biomaterials.

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Cellulose-Based Hydrogels in Topical Drug Delivery: A Challenge in Medical Devices

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Abstract

Drug delivery is a difficult task in the field of dermal therapeutics mainly in the treatment of burns, ulcers, and wounds. Therefore, fundamental research and the development of novel advanced biomaterials as hydrogels are ongoing to overcome these issues. Currently, several approaches are starting to emerge aiming the stabilization of drug loaded in hydrogel material by increasing the mutual interactions between the polymers, the polymers, and the drug and by covalently cross-linking the polymers during hydrogel formation. Hydrogels provide mechanical support and control over architecture, topography, and biochemical characteristics that make them functionally appropriate to biomedical materials. In this regard, cellulose-based biomaterials can be considered as a gold standard for many topical pharmaceutical applications because of their versatility in fabrication, biodegradability, and biocompatibility. In open wounds, a curative ideal hydrogel is proposed for occlusion and maintenance of the moist environment. Healing through the wet medium has comparative advantages such as preventing dehydration of tissue leading to cell death, stimulating epithelization and formation of granulation tissue, facilitating the removal of necrotic tissue and fibrin, serving as a protective barrier against microorganism, and avoiding excessive fluid loss and can still take drugs. On the other hand, another recent challenge is the use of hydrogel in the manufacture of microneedles. The microneedles are able to, with little force, penetrate effectively in the tissues, maintaining the continuous contact, without causing damages in the tissue, providing a high force of adhesion. These devices may be an alternative to the infection-resistant staples used in surgeries to attach skin grafts to patients with severe wounds resulting from burns and to be used in drug release. In this chapter, we discuss recent developments in cellulose-based hydrogels with respect to drug delivery and current applications in the new devices and research settings for infections, inflammations, skin burns, and wound treatment.

Keywords

Cellulose-based hydrogels · Dermal therapeutics · Drug delivery · Biomaterial · Devices

1 Introduction

Drug delivery is a new approach based on formulations, technologies, medical devices, and systems to transport molecules, like drugs, peptides, proteins, small molecules, and interferons, through the body and safely achieve its desired therapeutic effect at the target site. Moreover, localized drug delivery allows an easy self-administration for patients [1]. Besides this, localized drug administration avoids some metabolic issues such as the absorption by the gastrointestinal tract and the hepatic first-pass metabolism, improving the bioavailability and maintenance of the drug concentration during the treatment. Through this kind of system, the drug is administered at the desired concentration into the target site, which may further

reduce undesired side effects. Additionally, local delivery enables the increase of drug molecules in the target area, taking advantage of the increasing therapeutic potential and, subsequently, reducing systemic drug toxicity.

In this regard, the advantages of drug delivery systems (DDS) have been studied as a viable option to improve the properties of drugs in topical administrations, as well as to treat skin diseases and wounds.

Wound affects a large number of patients, being characterized as an interruption in the continuity of a corporeal tissue, which may be triggered by some trauma or by a condition that activates the body's defenses [2, 3]. Moreover, wounds are interruptions of cutaneous-mucosal integrity and result from imbalances in the health of people, which may prevent or hinder basic aspects of life such as locomotion [2, 3]. The wounds can be classified into chronic and acute [4].

Thereby, healing is a physiological process that proceeds from a series of cellular events culminating in the restoration of the functional integrity of tissues [5]. Wound treatment is usually based on topical therapies that are guided by cleansing, debridement, and use of dressings [6]. The dressing is considered all the materials placed directly over a wound, whose objectives are to avoid the contamination of clean wounds, facilitate healing, reduce infection in contaminated lesions, absorb secretions, facilitate drainage of secretions, promote hemostasis with compressive dressings, maintain contact of medications with the wound, and promote comfort to the patient [7]. Therefore, several studies have shown that natural polymers can facilitate the healing [8–10]. The study of Tummalapalli and colleagues is an interesting example of that, in which it used *Aloe vera* and curcumin loaded oxidized pectin-gelatin (OP-Gel) matrices as antimicrobial finishes on nonwoven cotton fabrics to produce wound care devices. The in vivo wound healing analysis was carried out using an excisional splint wound model in C57BL/6J mice. The results obtained showed, that in only 8 days, the OP-Gel-Aloe was able to promote a more fast wound healing in about 80% of the mice used [11].

Furthermore, the developed dressings can be opened or closed, and the closed or occlusive ones are subdivided into moist and dry [12, 13]. Wet dressings are intended to reduce the inflammatory process by vessel constriction; clean the skin of exudates, crusts, and scales; maintain drainage of infected areas; and promote healing by facilitating cell movement [7].

Hydrogels are polymeric materials with suitable properties to be used in the development of dressings. They consist in one or more three-dimensional structured networks, formed by macromolecular chains interconnected by covalent bonds or physical interactions that under specific conditions can absorb large amounts of water. In general, hydrogels can be divided into two distinct classes: conventional hydrogels and intelligent hydrogels, which are synthesized and functionalized from different monomers [14]. Intelligent hydrogels are polymeric materials that have the typical characteristics of a hydrogel, however, present distinct responses according to the external stimuli [15, 16]. An interesting feature of these systems lies in the facility with which they are able to bring together a sufficient mechanical strength to withstand physiological stress, with a

very similar flexibility to body tissues, providing high biocompatibility, but also have the capability to successfully help to minimize the potential for irritation in possible in vivo administrations [17, 18].

Thus, scientific works have produced an increasing number of promising pharmaceutical biomaterial possibilities for dermal and transdermal therapeutics [19–22]. These strategies include hydrogels that can be prepared by natural materials such as cellulose, using them as wound dressings when conjugated with new products frequently introduced to target different aspects of the wound healing process [23–25].

Biomaterials can be used in contact with the biological system, either temporarily or permanently, for the purpose of reconstituting, treating, or even replacing functions of the human body, as well as organs and tissues [26, 27]. Hydrogels are the main biomaterials currently used in wound healing, cartilage, wound dressing, and bone regeneration, although they also have an important role as carriers to deliver and release drugs into the human body through different pathways, such as the topical administration [27, 28]. Furthermore, hydrogels can be used as a dressing because they keep the tissue hydrated and can absorb the moisture from the wound exudate, providing cellular regeneration [29]. The use of biomaterials in the treatment of tissue damage is an area of research on the rise. Recent advances in wound therapy with biomaterials have allowed using a delivery method for open wound therapies with the additional benefit of providing local care during treatment. Due to the three-dimensional structure of the hydrogels, it is possible to incorporate active compounds that promote wound healing or increase biocompatibility in order to accelerate the healing process [30–32]. The ideal dressing should achieve a rapid healing at a reasonable cost. Besides that, an important feature of skin repair materials to take into consideration is the biocompatibility of the material [33].

Currently, there are many cases in which patients apply hydrogels for the treatment of acute and chronic wounds with promising treatment results [34].

Another option to perform drug targeting efficiently through a dermal application until the epithelium is microneedles (MNs). These formulations are a new technology used as DDS; MNs are less invasive and present a great perspective for transdermal use [35]. Solid MNs were the first type of system developed for the administration of transdermal drugs [36]. These systems are used for pretreatment of the skin, increasing its permeability and facilitating drug delivery [37]. When applied to the surface of the skin, they create MNs through which the drugs are transported by passive diffusion after removal of the MN. The drugs can be applied through a conventional transdermal system or using topical formulations such as ointments, gels, or lotions [36]. More advanced systems have been developed as coated, soluble, hollow MNs and formed by hydrogels [38–41]. The MNs synthesize by hydrogel have the potential to overcome the limitations of conventional MNs designs by considerably increasing the number of active molecules that can be delivered transdermally [41, 42]. In this sense, several studies have demonstrated the effectiveness of these MNs to increase the permeability of several molecules [11, 43].

1.1 Overview of Skin and Wounds

The skin can be characterized as the largest organ of the human body, presenting the following peculiarities: resistance, flexibility, relatively impermeable, ability to repair itself, and protect the body by informing you of environmental changes [44]. In an individual adult with average weight and height, the surface of the skin presented is 2 m^2, and the weight corresponds to 4.2 kg, receiving about a third of the blood circulating in the body. There are many functions of the skin as its sensory and immunological information capabilities, which it is able to be transmitted due to the high innervation and vascularization of the skin [45, 46]. Thereby, it is important to note that the skin includes sensory receptors that detect heat, cold, touch, pressure, and pain [45, 47]. The skin presents slightly acid pH (4.6–5.8), which contributes to bactericidal and fungicidal actions on its surface. Some important processes are involved in maintaining the balance of the skin surface, such as keratinization and lipids on the surface of the skin. The skin performs many functions, but in relation to human skin permeation, the most important function is protection. Other important roles are protection against pathogens, production of vitamin D that performs a function of high relevance at the bone level, and protection against ultraviolet radiation [48]. Regardless, the skin also has the function to prevent dehydration by reducing the loss of body water, through the conservation of the body homeostasis which is guaranteed by three processes, namely, the elaboration of metabolites, hemodynamic regulation, and thermoregulation, as well as the skin has the ability to eliminate small amounts of excretion products [45, 49].

The skin is subdivided into two layers: the epidermis and the dermis. The main cellular component of the epidermis is the keratinocyte, and the dermis is the fibroblast. The epidermis is a lining of epithelial tissue which supports several skin attachments such as hairs, nails, sweat glands that are responsible for the production of sweat, and sebaceous that produce sebum, forming a fatty film on the skin. This layer rests on the dermis. The main function of the epidermis is the production of cells that protect the skin against the outside environment [45]. Meanwhile, the dermis is considered a supporting tissue called connective tissue because it contains cells, fibroblasts, and fibers and is attached to the hypodermis. Hypodermis accounts for most of the structural strength of the skin and flexibility [50].

The epidermis and the dermis that constitute the skin rely on the hypodermis that unites it to the bones and the muscles supplying blood vessels and nerves [51].

Histologically, the epidermis is constituted with the basal, thorny, granular, lucid, and corneous layers, being an important sensory organ. The epidermis is firmly attached to the dermis by an adhesion area, the dermo-epidermal junction, and a basement membrane composed of collagen IV, structural glycoproteins, and proteoglycans [52]. In the dermis, the blood vessels, lymphatic vessels, hair follicles, sweat and sebaceous glands, hair, nerve endings, and cells, like fibroblasts, mast cells, monocytes, macrophages, plasma cells, and others are found [45, 51].

The hypodermis is also part of the connective tissues, with the purpose of storing lipid and fat stores that serve to feed the body in case of an increased energy needs or an insufficient diet [44, 50].

When a skin injury occurs, some mechanisms are activated that enable the regeneration and the reparation of the skin [53]. The healing of a wound is defined as a physiological process through which the organism manages to restore the functions of the damaged tissues [54].

Wounds are the result of an aggression by an agent to living tissue [3]. Wounds can be classified in several ways by the type of causative agent, according to the degree of contamination, the time of trauma, and the depth of the lesions, being the first two mentioned as the most used [54]. In this regard, wounds can also be classified according to the degree of contamination [55]. This classification is important because it guides the choice of the drug treatment used [55, 56].

After an injury to a tissue, dynamic phenomena known as scarring begin immediately, which is a sequence of responses given by the most varied type of cells (epithelial, inflammatory, platelet, and fibroblast), which interact to restore tissue integrity [5, 29]. The type of injury also has importance in the type of repair; thus, in a clean surgical wound, there is a need for the minimal amount of new tissue, whereas, for example, in a large burn, there is a need for all the organic resources for healing and defense against an infection [55, 57].

Wound healing is performed through four distinct phases: vascular, inflammatory, proliferative, and maturation or remodeling [3, 54, 57]. The vascular phase is dependent on platelet activity and the coagulation cascade. It is the first phase that occurs after the onset of the wound. The inflammatory phase is described by the invasion of fibroblasts that proliferate and secrete the tissue-specific repair proteins. In the inflammatory phase, neutrophil migration from the blood vessels to the wound will occur, which will be mediated by the binding to super expressed endothelium-activated selectins. In the proliferative phase, regeneration of connective tissue and epithelium occurs. At the end of maturation or remodeling, the deposition, clustering, and remodeling of collagen and endothelial regression occur [28, 53, 54, 57]. The purpose of reepithelialization is to restructure the functions of the epidermis that were lost with the occurrence of the lesion: mechanical protection, local temperature regulation, defense against microorganisms, and water barrier.

Moreover, most healing wounds are called acute wounds [4]. The main cause in our environment is injuries, followed by thermal, infectious, chemical, vascular, allergic, and radioactive wounds [3, 4]. An acute wound may be chronic, as long as some mechanism interferes with its physiological healing process [3, 57]. Chronic wounds can be defined as a visible disruption in the body surface that cannot heal or require a long time to heal. They are wounds where their repair process has failed [3, 4]. Chronic wounds distinguish themselves by size and nature, and some may heal in months and others in years [58]. The most common chronic wounds are venous leg ulcers, pressure ulcers, and diabetic foot ulcers [4, 59, 60]. Leg ulcers are caused by continued venous hypertension; this problem may arise due to changes in the venous, arterial system and may also be associated with diabetes or rheumatoid arthritis [59, 61, 62].

Treatment, whether for chronic or acute wounds, should be performed in an individualized way, taking into account the evolution of the condition, the

occurrence of factors that cause changes in the prognosis, the physical characteristics of the wound, and the availability of resources [2, 58, 63].

2 Classification of Cellulose Derivatives

Cellulose is the most common organic compound in nature. It constitutes between 40% and 50% of almost all plants. Cellulose is also present in bacteria and algae but in small proportions. The bacterial cellulose is produced mainly by bacteria of the genus *Gluconacetobacter*, *Rhizobium*, *Sarcina*, and *Agrobacterium*, being the species *Gluconacetobacter xylinus* as one of the most efficient and most used in its production. Cellulose is a polysaccharide which is presented as a straight chain polymer of sufficient length to be insoluble in organic solvents, water, acids, and alkalis diluted, at room temperature, consisting solely of β-D-glucopyranose units, which bind through the carbons β(1–4), having an organized and partially crystalline structure. The cellulose structure is stabilized by hydrogen bonds bridging the hydroxyl group of the C3 and O position of the adjacent glycosidic ring and between the hydroxyl group of C2 and the hydroxyl group of C6. The stabilized acetal bonds between the anhydroglucose units, which have a rotation of 180° in the plane, and the adjacent units form units called cellobiose. In nature, the cellulose chains aggregate to form the elementary fibrils, a bundle of filiform chains stabilized by the hydrogen bonds established between the hydroxyl groups of adjacent chains [64]. The elementary fibrils are successively added to form microfibrils, macrofibrils, and finally the cellulose fibers [64, 65]. The cellulose chains have a high tendency to form semicrystalline fibers, and it is possible to determine their structure by X-ray diffraction [66]. Although at least four forms of cellulose are known as I, II, III, and IV [64].

Cellulose has many uses, from antifouling, emulsifying, stabilizing, dispersing, and thickening to gelling agents, but these are secondary to the most important use which is the ability to retain water [67].

Water cannot penetrate the crystalline regions, but the amorphous dry region can absorb water and become soft and flexible [64, 68, 69].

Bacterial cellulose (BC) has shown high efficiency as a material for the treatment of wounds and burns since it significantly improves several aspects during the curing process, and its properties such as high water absorption capacity and high mechanical strength and biocompatibility make BC particularly suitable for its use in this clinical setting [70]. An important feature of skin repair materials is their ability to absorb the exudate during treatment as well as the ease of removal of this material after recovery [7, 28]. The materials typically used such as the gauze are permeable and absorbent but may readily adhere to the surface of the wound and induce trauma during removal, while BC treatment allows them to be removed without damage. The BC membranes still have several other advantages over the conventional methods, namely, excellent moldability and adherence to wound sites even in

the most difficult areas, like the nose, mouth, and hands, and, in large areas, the ability to keep the media moist, the ability to significantly reduce pain and accelerate reepithelialization, and the ability to absorb exudate and reduce scar formation [71–73].

Cellulose is an extremely abundant natural polymer with a vegetable origin, but its restricted solubility to specific solvents limits its applications. The presence of the hydroxyl groups in the cellulose structure provides an important characteristic related to its reactivity. That is, these groups favor the occurrence of various organic reactions such as nitration, acetylation, and esterification, for example, allowing the easy production of aqueous-soluble cellulose derivatives [74]. With the chemical modification of cellulose, one can obtain derivatives with solubility in organic solvents and mainly in water, as carboxymethylcellulose (CMC), methylcellulose (MC), and hydroxyethyl cellulose (HEC). The cellulose derivatives have chemical and physical properties strongly influenced by the type of substituent, degree, and uniformity of substitution, among other aspects [64, 74, 75].

2.1 Carboxymethylcellulose

CMC is a derivative of cellulose obtained by the chemical modification of the natural structure of cellulose like it is schematically represented in Fig. 1 [76]. CMC, one of the most important derivatives, is highly soluble in water, allowing its use in the pharmaceutical, cosmetic, biomedical, food, paint, and adhesive industries [77, 78]. Due to the property of forming films, biodegradability, and biocompatibility, CMC has had applications as wound dressing and artificial skin.

2.2 Methylcellulose

MC is water soluble, and it is used in a wide range of applications, mainly due to its colloidal properties in aqueous solutions [79]. The degree of substitution of MC is defined by the average number of hydrogen atoms of the hydroxyl groups, which are replaced by methyl groups in the anhydroglucose units. In Fig. 2 the chemical representation of MC material is described.

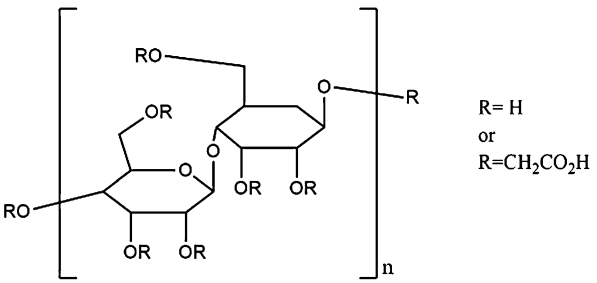

Fig. 1 Schematic representation of the cellulose derivative CMC

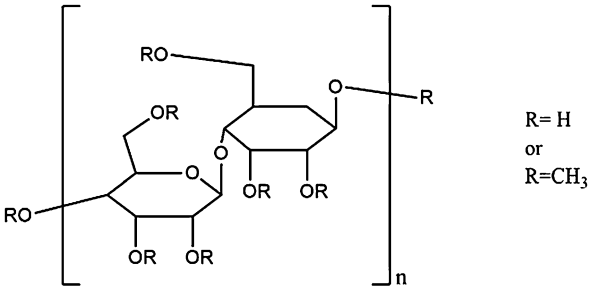

Fig. 2 Schematic representation of the cellulose derivative MC

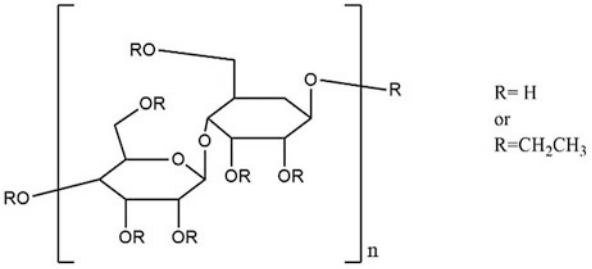

Fig. 3 Schematic representation of the cellulose derivative EC

Li and Boehnke after their studies on the cornea epithelial of pig's eyeball concluded that MC is able to accelerate the corneal epithelial wound healing [80].

2.3 Ethyl Cellulose

Ethyl cellulose (EC), a derivative from cellulose, is a hydrophobic biocompatible polymer, soluble in a wide variety of organic solvents, nontoxic, colorless, odorless, well-formed with mechanical strength, very stable in most environmental conditions, and insoluble in water and gastrointestinal medium. EC is a polymer with a broad application in feed, cosmetics, and pharmaceutical area [74]. A series of bio-composites including poly3-hydroxybutyrate-grafted ethyl cellulose stated were synthesized. After characterization of biodegradability, cytocompatibility, and antimicrobial activity, the authors suggested that the bio-composites have great potential to use in wound healing, covering the affected skin area which may favor tissue repair over smaller times [81]. Thus, in Fig. 3 the structure of this viable cellulose derivative is presented.

2.4 Hydroxyethyl Cellulose

HEC has a hydrophilic polymeric backbone like it is shown in Fig. 4. Its structure is soluble in an aqueous medium due to the presence of hydroxyethyl groups. The synthesis of HEC is made from cellulose in the presence of sodium hydroxide and

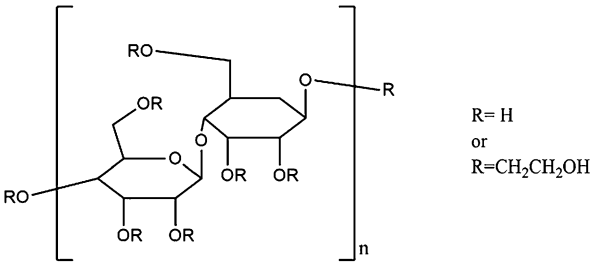

Fig. 4 Schematic representation of the cellulose derivative HEC

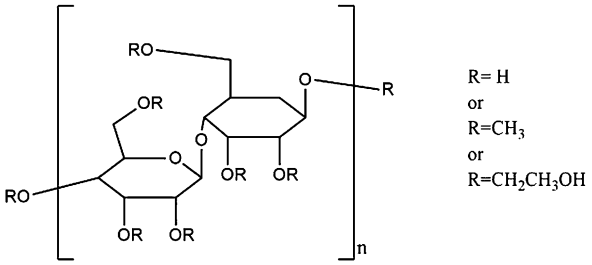

Fig. 5 Schematic representation of the cellulose derivative HPMC

ethylene oxide [82]. It is easily soluble in hot or cold water forming clear solutions with a wide range of viscosities. Marcos and coworkers studied supramolecular gels of poloxamer-hydroxyethyl cellulose (HEC)-α-cyclodextrin to obtain synergisms regarding solubilization and sustained release of griseofulvin for topical application. The combined effects of the poloxamer and the HEC with cyclodextrin prevented phase separation and led to supramolecular networks that solubilize and controlled the antifungal drug. It has also showed the rheological and bioadhesive properties of gels loaded or not loaded with the drug, which could be easily tuned when it was modulated with the polymer's proportions [83].

2.5 Hydroxypropyl methylcellulose

Hydroxypropyl methylcellulose (HPMC) is a cellulose ether wherein the hydrogens and the hydroxyl groups of the cellulose were partially replaced by alkyl or by alkyl-substituted groups modified with the characteristics of the native cellulose (Fig. 5) [84]. It is stable in the presence of heat, light, air, and moisture; and it has the ability to form a gel in an aqueous medium. Agubata and colleagues developed and evaluated in vivo wound healing activities in rats using excision wound model and histological examination. Results showed that drug-loaded hydrogels containing dilute microfibers of the sutures promote a reduction of 95% in size of the wound after 14 days. They showed that the materials induced high collagen deposition after 21 days of wounding, with minimal scar formation. They concluded that drug

hydrogels containing HPMC and micronized suture fibers can be applied for effective wound healing [85].

3 Formation of Cellulose Derivative-Based Hydrogels

Hydrogels are polymeric materials which, through cross-links, form a three-dimensional hydrophilic network of polymer chains. The main characteristic of these materials is the ability to absorb and retain water without suffering dissolution [86]. Hydrogel polymers are those capable of retaining between 20% and 100% of water in relation to their total weight. The absorption and diffusion of solutes through the hydrogel polymer network is determined by its swelling. The most efficient polymer materials to absorb water are those that carry a certain ionic character in their structure since repulsion is important to promote swelling of the polymer in the aqueous fluids. The mechanism of water absorption by the dry hydrogel begins with the hydration of the polar and hydrophilic groups. When the polar groups are hydrated, the network expands and exposes the hydrophobic groups, which can also interact, via van der Waals forces, with the water molecules. After the hydrophilic and hydrophobic sites interact with the water molecules, the polymer network absorbs an additional amount of water due to an osmotic force carried by the network toward infinite dilution. This further expansion is limited by covalent cross-links, thus leading to an elastic retention force in the chain reaching equilibrium. Despite the great advantage of being synthesized by nature, cellulose is not soluble in conventional organic solvents, and the introduction of less polar groups into its polymer chains is quite common. Researchers have been focused on the dissolution of cellulose to provide improvements in its solubility characteristic [87–90]. It is important to note that the type of cellulose influences its solubilization form. Cellulose derivatives have been used to prepare cellulose-based hydrogels through physical and chemical cross-linking. Physically cross-linked hydrogels are formed by physical interactions such as electrostatic associations, hydrogen bonding, van der Waals forces, or an associative polymer-polymer interaction [91]. On the other hand, chemical cross-linked hydrogels are produced by covalent bonding formation between two or more kinds of polymer chains in the presence of a chemical cross-linker or under irradiation [92]. When a correct cross-linker and cellulose concentrations are used, it is possible to control the hydrogel mechanical properties and swelling capabilities [93]. The cross-linking agents are multifunctional compounds which may contain at least two polymerizable double bonds, at least one polymerizable double bond and a functional reactive group with the monomer, and at least two functional reactive groups with the monomer and polyvalent metals capable of forming ionic cross-links [94].

The physical properties of the polymer can be affected by adding cross-links, and it is dependent upon the degree of cross-linking and the presence or absence of crystallinity [95]. Some properties should be controlled, such as:

- Elasticity, since they can stretch and return to their original form. As the number of cross-links increases, the polymer becomes more rigid and cannot stretch as much.
- Decrease in the viscosity, in other words, the resistance to the flow of polymers.
- Insolubility of the polymer. Cross-linking results in insolubility as the chains are tied together by strong covalent bonds. Cross-linked materials cannot be dissolved in solvents but can absorb solvents.
- Increased Tg and increased strength and toughness. Cross-linking changes the local molecular packing, resulting in a decrease of free volume, leading to an increase in Tg.
- Transformation of thermoplasts into thermosets [95].

Due to the recent developments and due to the growing importance of versatile biomedical materials, such as hydrogels derived from cellulose, it has raised a renewed interest in the field of medical devices involving healing material and drug delivery [23, 33, 96].

3.1 Physical Cross-Linking

At low concentrations, polymer solutions are isotropic; however, when the polymer concentration increases, the transition from liquid to gel takes place followed by gelation into a solid gel with isotropic structure. This structure becomes more organized with the increase of polymer concentration due to the formation of more hydrogen bonds [97]. Physically cross-linked hydrogels can be synthesized by some methods as ionic interaction, crystallization, hydrophobized polysaccharides, and hydrogen bonds [95]. In the case of hydrogen bonds, hydrogels are synthesized through the formation of hydrogen bonds between the polymers, being this only possible when a carboxylic acid group is protonated, which is related to the pH-dependent capability of the hydrogel to swell. Another method of physical cross-linking is the crystallization, which can be subdivided into ionic interactions and stereocomplex formation [98]. Thus, in the last years, some works have identified the hydrogels formed through physical cross-linking as better options in relation to the chemical cross-linked hydrogels; this is because physically cross-linked hydrogels normally have low toxicity, being the toxic compounds removed before the application [99]. Therefore, for biomedical applications, physical cross-linking has the advantage of avoiding residual amounts of cross-linking agents which could be toxic to the body. Another method for producing physically cross-linked hydrogels is the cryo-gelation method [100, 101]. The gelation method is performed through the establishment of hydrophobic bonds, that is, with the increase of temperature, hydrogels lose their water and start to form hydrophobic bonds between the polymers which, consequently, lead to the development of the hydrogel structure. This process is dependent on the temperature, the number of substitution degree of the cellulose derivatives, and the addition of salts [102].

3.2 Chemical Cross-Linking

The development of chemical cross-linked hydrogels implies the presence of compounds used as cross-linkers, in order to covalently bind different polymeric molecules in a three-dimensional network. In this regard, for applications in the food and the pharmaceutical industry, as well as to be used as biomaterials, it is necessary to develop biocompatible cross-linkers [92]. Chemical cross-linked hydrogels are synthesized by chain growth polymerization, through free radical-controlled free radical polymerization, anionic and cationic polymerization, and by polymerization caused by addition and condensation, which involves the stepwise addition of polyfunctional cross-linking agents with monomer functional groups, and by gamma and electron beam polymerization, which involves high energy electromagnetic irradiation as a cross-linker. The chain growth and gamma polymerization involve three steps, namely, the initiation, propagation, and termination as in the free radical polymerization [95].

In spite of this, cellulose-based hydrogels can be developed by chemical cross-linking, which normally requires esterification or etherification of the cellulose hydroxyl groups. These modifications usually lead to more beneficial cellulose derivatives to be used in a wide variety of industries [99]. The formation of cellulose-based hydrogels through chemical modifications can lead to irreversible cross-links in the cellulose structure, being the degree of cross-linking directly related to the number of cross-linking of the polymer structure. This cross-linking degree can influence the properties of the hydrogel, like their mechanical and degradative characteristics, although this can be relatively controlled during the chemical synthesis process [102]. Thereby, the cross-linker agents and the number used to form hydrogels are dependent on the cellulose derivative that is used. Some of the most used agents are toxic in their unreacted form, like the aldehydes, and for that should be avoided in order to maintain a sustainable process and a biocompatible hydrogel [102].

4 Properties of Cellulose Derivative Hydrogels

Cellulose derivative-based hydrogels are optimal materials to be applied in a wide variety of biomedical applications, which can be due to its biocompatibility, excellent mechanical properties, transparency, high water content, and low cost. In this sense, the type of cellulose used in the hydrogel formulation can influence the rheological behavior and the physical stability of the hydrogel. One of the physical properties is the variation in the hydrogel volume as a response to any external stimulus that causes changes in these properties, such as water absorption kinetics, polymer network permeability, and pore size, which, consequently, can affect the drug release by these polymers network [24, 103, 104]. The sol-gel transition is a characteristic of cellulose derivative hydrogels, as they are thermoreversible, and it is dependent on several factors, including polymer concentration, pH, and temperature [23, 105, 106]. Many of the compounds having the solution transition temperatures

present formation of gels with the reduction of the temperature. However, certain aqueous solutions of cellulose derivatives having a balance between hydrophilic and hydrophobic functional groups may undergo gelation processes at high temperatures. That is, the temperature at which occurs the transition between the liquid state and the gel state depends on the degree of substitution of the hydroxyl groups in the cellulose structure, being observed in an increase in the polymer-polymer interactions with the increase of temperature. MC and hydroxypropyl cellulose (HPC) are typical examples of gel-forming cellulose-based materials at high temperatures [107]. The rheological behavior of a cellulose-derivative hydrogel can be influenced by the type of cellulose that is used and its behavior as to the desired application [108, 109]. In this way, when the developed hydrogels are intended to be used as a DDS in a topical administration, it is important to consider the rheological properties of this hydrogel. This is because the mechanical characteristics of a hydrogel to be used in a topical therapy have influence in the development process, packing, and storage. Besides this, this type of properties is also dependent on the concentration of the polymer used, their structure, and the number of cross-linking modifications. Thus, cellulose-based hydrogels have a semisolid three-dimensional gel structure with a high strength, directly related with the existent number of cross-linking between the polymers, being this viscosity form of hydrogels reversible, and it can be altered with the increase of temperature [23]. All these factors turn cellulose-based hydrogels into a good candidate to transport drugs in a dermal application, since they have nontoxic compounds, which were washed during the cross-linking process, they are water soluble, and their rheological and mechanical properties allow the high strength gel to transport drugs in their matrix and release them in the contact with environmental changes, such as the increase of temperature [23, 102, 105, 106].

5 Cellulose Derivative Hydrogels as Drug Delivery Systems

Over the years, researchers have been looking for suitable and promising alternatives for drug administration, in order to improve the biodistribution and bioavailability of drugs in vivo and, consequently, to improve the dose-response relationship. In this sense, DDS arise as a promising strategy to overcome the biological barriers and to perform an efficient drug delivery, in which hydrogels have gained a lot of interest in the pharmaceutical field [23, 110].

In this regard, hydrogels are represented as a semisolid form with a three-dimensional structure composed of hydrophilic compounds, being capable of swelling and absorbing large amounts of water in their structure [91, 111, 112]. Lately, these types of vehicle have been extensively studied with a focus on the use of derivatives of natural polymers as DDS to be applied in different routes of administration, which can be attributed to their attractive advantages, like nontoxicity, the capability to incorporate drugs with poor solubility, good bioadhesive properties, high water solubility, and swelling-deswelling relation [23, 111, 113].

Moreover, these unique properties of hydrogels as efficient DDS can be explained by their physical structure, since they have a high porosity, promoting an affinity to

an aqueous environment. This is mainly attributed to the capability of these structures to swelling, which also favors the loading of drugs in their matrix, consequently, improving pharmacokinetics by releasing drugs in a controlled and slowly rate for a long period of time, maintaining a higher dose of the drug in the site of action. Besides this, hydrogels are also biocompatible, due to their structure with a high amount of water and chemical similarities with the extracellular matrix, and they have adhesive properties that allow an easy adaptation and application on the surface where the hydrogels have to be applied [114]. In addition, hydrogels can be considered stable structures, depending on the chemical interactions in their matrix, and structures easily degradable and dissolved after application [115]. In this sense, all these beneficial physicochemical characteristics of hydrogels have sustained the thought and research of this biomaterial as a stable and efficient DDS to improve the properties of drugs and, subsequently, the treatment used.

In this way, during this chapter, it was described the known cellulose derivatives and its improved characteristics to form hydrogels as DDS. Thus, there exist two main groups of cellulose derivatives, namely, ethers and esters, in which the cellulose derivative ethers have been used for awhile in the pharmaceutical industry as excipients, being the following examples include some of these derivatives, MC, EC, HEC, CMC, HPC, and HPMC [91, 111]. Therefore, several works have been performed with the goal to show that cellulose derivative-based hydrogels have the capability to do an efficient drug delivery and a controlled drug release, being one example is the work of Chang and colleagues. In this research work, the authors have developed a formulation of a hydrogel based on cellulose and CMC in an aqueous system of sodium hydroxide and urea, in order to study and to obtain a superabsorbent carrier with high capability to swell and to reverse this behavior in adverse conditions, as the presence of inorganic salts in urine. Then, the results obtained by them show a hydrogel with the capability to incorporate drugs and reversibly alter their structure to promote a controlled drug release in specific physiologic conditions, which turns this hydrogel into a smart swelling carrier with important features of biomaterials for drug delivery [116].

6 Therapeutical Applications

As aforementioned, cellulose derivative-based hydrogels have been extensively studied as a promising DDS to improve the bioavailability of drugs, as well as to promote a more efficient treatment. In this section, some of the therapeutic applications of hydrogels composed of cellulose derivatives will be described.

6.1 Controlled Release

The known cellulose derivative ethers are hydrophilic, biocompatible, and biodegradable and form a hydrogel when absorbing high amounts of water. These hydrogels can incorporate in their network drugs or other therapeutic biomolecules,

releasing them at the site of interest by drug diffusing after changes in the environmental conditions, such as variations in pH and temperature [111]. These cellulose derivatives have suitable characteristics to do a targeted and sustained drug release over a long period of time, which can be explained by the capability of its matrix structure to diffuse or to dissolve in the presence of a specific environmental stimulus; besides this a more accurate targeted release and a controlled drug delivery in the specific site/target can be performed by gel structures that reversibly change when in contact with a specific trigger, like the change of pH [117]. Although, these characteristics are dependent on the material used, the chemical cross-linking, and the mesh size of the hydrogel [111]. Therefore, more advanced and smart hydrogel-based DDS with cellulose derivatives have been developed that can bind the drug in their network by covalent or physical linkages to further control the release profile of the drug, through transitions of swelling and deswelling with alterations in the mesh size of the hydrogel, as well as taking advantage at the body temperature and the variable pH ranges in the different body parts, and to do a space-controlled drug release [118].

Thereby, for the past years, controlled drug delivery has been used for an oral administration, being the example is the work of El-Hag Ali and colleagues, in which they used a CMC-based hydrogel to deliver the drug theophylline in a specific way into colon target cells, taking advantage of the variable pH range and the ionic strength [119]. In addition, other studies suggest the delivery of cellulose derivative-based hydrogels loaded with the therapeutic molecule through the use of injectable formulations, once these hydrogels have an interesting property, namely, the capability to maintain their chemical structure without modifications when injected, promoting a controlled drug delivery. In this sense, HPMC has been extensively studied as cellulose derivative-based hydrogel on delivering therapeutic biomolecules in vivo, through injectable formulations [120, 121].

Regarding this, several cellulose derivatives, like the solubles HPMC, CMC, and MC, have been used to deliver drugs efficiently through an intranasal administration, because these systems present good mucoadhesive properties, which improve the absorption of drugs, but also due to the increased viscosity which promotes the sustained drug release by these hydrogels [122]. Therefore, several works have proven the efficacy of these systems on increasing the bioavailability of drugs when delivering them by an intranasal pathway [111, 123].

However, hydrogels have been more studied and highlighted as a matrix to be used in tissue engineering and as a gel or ointment to be applied in dermal applications. In this manner, recently, the skin has received a lot of attention as a viable route of administration, not only for skin diseases but also to treat other pathologies, since this pathway is easier to apply and painless, turning them a more acceptable route of administration for the patients [23]. Thus, drug delivery through topical administration has been considered an attractive option, mainly to avoid the biological barriers, like the passage by the gastrointestinal tract in the oral administration [91].

Moreover, the drug administration focus in this chapter consists of the topical application of cellulose derivative-based hydrogels as DDS, taking advantage of the

suitable characteristics of these hydrogels in order to improve the drug properties in vivo and, subsequently, to develop a more efficient treatment avoiding the side effects of the conventional therapeutic.

6.2 Wound Dressing

Wound dressings are widely used in medicine and pharmacology to treat a defect or break in the skin caused by a physical damage or resulting from a physiological condition of the patient. Wounds can be classified taking into account the level of damage since the skin has various layers. In this form, it is necessary to develop a process to treat and repair skin, taking into consideration the number of skin layers affected [124, 125].

By these means, hydrogels are attractive candidates to treat this type of malignancies, since this kind of ointment favors the healing of skin defects, as well as presents properties that confer protection of the wound while healing but also due to the non-adhesiveness, easy use, and elimination of these hydrogels [126]. Wound dressing strategies by using natural polymer derivative-based hydrogels have given an ideal form of skin treatments, basically, because these hydrogels can be synthesized in their matrix with antibiotic drugs and antimicrobial agents leading to a double therapeutic effect through the treatment of the skin defect and preventing new infections by microorganisms [127]. Therefore, several hydrogel formulations as wound dressings have been developed, by using natural, synthetic, or a combination of both types of polymers, and several of these formulations have been patented and present good therapeutic results.

Thus, there have been researchers working in the development of novel wound dressing formulations with better properties and improved treatment results, being cellulose derivative-based hydrogels as one of the most promising options [128–130]. Currently, there is a need to overcome the time and dose required to treat a wound, and these hydrogels have the capability to respond to environmental stimuli, like the temperature, releasing the drug in a sustained way and, consequently, improving the healing process with an accelerated process. Thereby, cellulose derivative-based hydrogels present the accurate properties to be an ideal dressing for a wounded skin, since they can protect the defect against undesired contaminations, as well as they have the capacity to maintain a constant temperature, promoting a faster healing and a reduced pain [131]. Besides this, they are not allergenic, adherent, and toxic, being easily removed and washable like it had been mentioned in Sect. 5 of this chapter.

In this regard, it exists some commercially available hydrogel mixtures based on cellulose derivatives available to treat wounds. Some of these commercial hydrogel formulations available are constituted by CMC or sodium CMC as the hydrogel from Smith and Nephew, named IntraSite™ Gel, which is used to take out the hard-boiled tissue from the wound and promotes the quickly wound healing in a unique application. Another hydrogel was the Silvercel™ from Johnson & Johnson normally used with the goal to avoid microbial infections in chronic wounds, like ulcers

Table 1 Types of various cellulose hydrogels and their important biomedical applications in wound care

Cellulose hydrogel composition	Model drug used	Biomedical application	Reference
Carboxymethylcellulose/cl-poly (lactic acid-co-itaconic acid)	Amoxicillin	Excellent antibacterial agent against gram-positive *Staphylococcus aureus*	[132]
Polyvinyl alcohol/sodium carboxymethylcellulose	Propolis	Wound healing	[133]
β-cyclodextrin/ carboxymethylcellulose	Acyclovir	Controlled drug delivery systems	[134]
Succinyl chitosan/ carboxymethylcellulose	Hydrogen peroxide	Bioactive antimicrobial hydrogel system	[135]
Cellulose/halloysite	Curcumin	Strong inhibition effect on the cancer cells and anti-inflammatory wound dressings	[136]
Hydroxyethyl cellulose/poly (β-cyclodextrin)	Eugenol	Potential advantage as efficient bacteriostasis against *Escherichia coli*	[137]
Carboxymethylcellulose/ pullulan	–	Decrease of postoperative tissue adhesion	[138]
Cyclosophoraose/cellulose hydrogels	Galangin	Efficient antibacterial dressing material	[139]
Hyaluronic acid/hydroxyethyl cellulose	Isoliquiritigenin	Improved the delivery of ILTG into the skin and potential as a transdermal delivery system	[24]
Poly(N-isopropylacrylamide)/ cellulose nanocrystals	Metronidazole	Good drug-loading capacity and promising materials for wound dressing	[140]

or chirurgical wounds. GranuGel™ and Aquacel Ag™ from ConvaTec are other examples of hydrogels to treat full-thickness wounds and avoid microbial infections, respectively, and Granuflex™ is a hydrogel to decrease the healing time of a superficial wound [111]. In relation to this, nowadays there is an increasing number of studies with the aim to develop new hydrogel formulations with improved action to treat wounds and skin defects. In Table 1 examples of biomedical applications of cellulose-based hydrogels in wound care are described.

6.3 Dermal Drug Delivery

The treatment of mild to moderate skin conditions or even a chronic wounded is, normally, realized through a dermal administration of the drug. In that way, therapeutic formulations of hydrogels as DDS have been used to treat inflammations and other skin diseases like eczema, psoriasis, and others, once these carriers can entrap

the drug and perform a percutaneous delivery [23]. Therefore, normally, hydrogels are composed of two main constituents, the gelling agent and the drug suspension, in which the gelling agent, such as the cellulose derivatives, is responsible for creating the matrix network where the drug would be entrapped, presenting physicochemical properties that allow releasing the drug in a controlled way, as well as promoting an increase of the drug bioavailability. In this sense, the properties of cellulose derivatives as gelling agents turn them as an attractive choice to be applied in a dermal drug delivery strategy [114, 141, 142].

Moreover, in the previous subsection, the capability of hydrogel formulations was also mentioned based on cellulose derivatives to treat skin defects and burned tissues as wound dressings, being the results obtained are very effective and positives, which came to prove once more the fact that these formulations have suitable characteristics to be used in topical administrations [143].

In this regard, researchers have been studied the development of cellulose derivative-based hydrogels as vehicles to transport therapeutic compounds, such as antimicrobial agents, in order to improve their viscosity and, subsequently, their efficacy in a cutaneous application.

The work of Sabale and coworkers is an example of an HPMC-based hydrogel to deliver a microemulsion of the drug bifonazole, with the main goal to improve drug solubility and permeability in the skin. Thus, these scientists have proven that the incorporation of this drug in a hydrogel matrix was able to promote an increase of skin permeability with the advantage of having a sustained drug release. In addition to these results, they also obtained an improvement in the stability of the developed hydrogel, as well as an antimicrobial activity, when compared with formulations available in the market [144].

Another research work is the one performed by Jantharaprapap and colleagues, which intends to show the benefits of using cellulose derivative-based hydrogels to incorporate nonsteroidal anti-inflammatory drugs with poor solubility, like meloxicam. Therefore, they were able to develop an HPC-based hydrogel containing permeation enhancers to incorporate meloxicam and, consequently, to improve their solubility and permeability characteristics, which allows the possibility to deliver meloxicam in effective therapeutic amounts through skin administration with an improved dose-response relation [145].

In addition, Hosny and colleagues intended to solve the problem of the gastrointestinal side effects and short half-time of the nonsteroidal anti-inflammatory ketorolac tromethamine with the development of cellulose derivative-based hydrogel. That is, this group incorporated this drug into a novel hydrogel formulation and performed a dermal administration, avoiding the painful side effects and multiple administrations. The results that they obtained show a controlled drug release, which is dependent on the concentration of the polymers used, but also an improvement of the anti-inflammatory activity [146].

Kouchak and coworker also develop a research work with the main goal to develop a hydrogel containing HPMC to incorporate the drug aminophylline and improve its absorption by the skin through a dermal administration with a resource to permeation enhancers [147].

Table 2 An overview of the studies about cellulose derivative-based hydrogel as DDS to improve drug bioavailability and treatment efficacy

Cellulose derivative	Drug	Treatment	Reference
CMC	Diclofenac (NSAID)	Skin wounds	[149]
HPMC	Etoricoxib (NSAID)	Chronic or acute illness	[150]
HPMC	Fluconazole (antifungal drug)	Skin fungal infections	[151]
HPC	Lidocaine (local anesthesia)	Promote a systematical and controlled drug	[152]
HPMC	Mepivacaine (local anesthesia)	Relieve local pain and perform a controlled drug release	[153]
CMC	Berberine (natural anti-inflammatory)	Protect postsurgical tissue and perform a controlled drug release	[154]
HPMC	Propranolol (nonselective beta-blocker)	Improve percutaneous penetration	[155]
HPMC	Propranolol (nonselective beta-blocker)	Improve drug release	[156]

Lastly, the research work of Arunkumar and colleagues is another example of the advantages of using a cellulose derivative hydrogel as a drug delivery carrier to overcome the poor properties of drugs, as well as, taking advantage of the biggest organ in the human body through an easy topical administration. That is, these researchers were able to obtain better and improved results for the drug, diclofenac sodium, bioavailability, and treatment effect after a dermal application of this drug when incorporated in an HPMC-based hydrogel containing permeability enhancers [148].

Moreover, in Table 2 more examples of cellulose derivative-based hydrogels as carriers to deliver different drugs through a dermal application are described.

Hence, cellulose derivative-based hydrogels due to their interesting properties have been studied and developed to be used as a delivery system in topical applications as shown in the scheme represented in Fig. 6. This can be justified by the fact that these hydrogels have the capability to improve the properties of drugs, allowing a higher treatment efficacy, through a noninvasive therapy with an easier and painless administration, which turn these hydrogels into a very promising form of dermal drug application.

6.4 Hydrogel-Forming Microneedles

Aside from the applications of cellulose derivative-based hydrogels previously described for dermal applications, the hydrogel-forming MNs arise. The MNs are small devices with a needle-like structure with dimensions in the order of

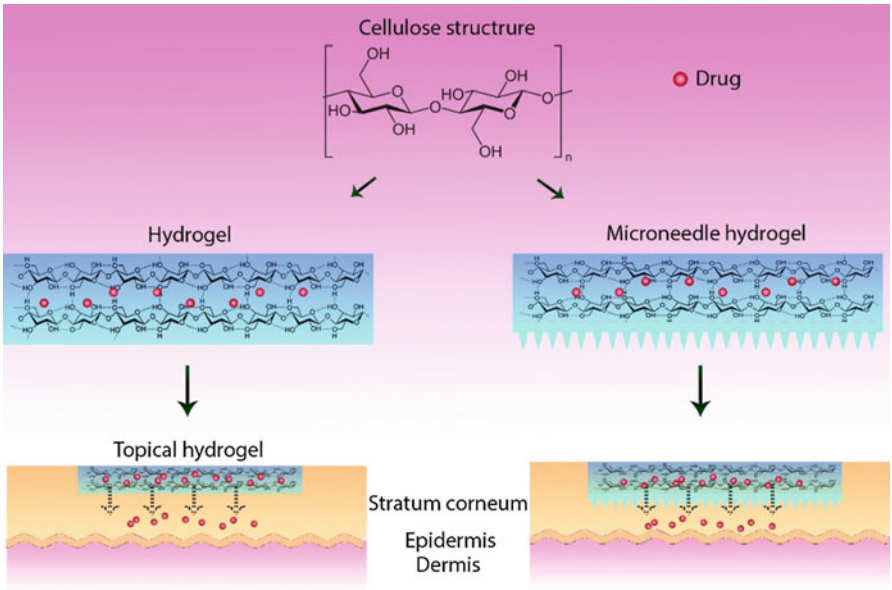

Fig. 6 Schematic representation of a cellulose-based hydrogel in topical drug delivery systems

micrometers, presenting a length around 25 μm and a height of 2000 μm. They are produced through numerous manufacture techniques using different geometries and various materials such as silicon (dioxide or nitride), metal (stainless steel), glass, ceramics, and polymers [157]. MNs are used to pierce the skin, promoting the stratum corneum disruption and creating transient micropores that facilitate the transport of drugs to the epidermis or dermis, with a minimum pain and invasiveness. Therefore, hydrogel-formed MNs create an integrated system consisting of a set of polymeric MNs projected from a solid base, attached to an adhesive reservoir containing the drug to be administered [41, 43]. Furthermore, with the application of the hydrogel-formed MNs, there is no obstruction of the MN channels by the tissues of the dermis, promoting a better control of the release profile of the drug and, consequently, enhancing the transdermal permeability. In this sense, Nayak and coworkers developed MNs to assist the permeation flux of lidocaine using sodium CMC/gelatine hydrogel. The MN hydrogel loaded with lidocaine was able to improve the skin permeation of the drug in the minimum therapeutic permeation threshold just after 70 min [158]. This makes hydrogel-forming MNs appealing as a controlled release device for administrations over prolonged periods of time. Recently, several researchers have been devoting their work to the development of MNs with reduced invasiveness and a large-capacity to perform a target delivery of drugs with great effectiveness [37, 40]. This technology has potential not only for the delivery of a wide range of molecules but to be applied in a variety of applications, namely, disease treatment, diagnosis, and palliative care [35, 36, 41, 159].

7 Conclusions

Clearly, cellulose-based hydrogels offer attractive advantages to deliver a wide range of therapeutic agents through a dermal application. Some of these consist in a fast and easy administration of the drug, as well as a sustained therapy through a specifically designed controlled release of the drug, which is considered a significant advantage in a topical administration. Therefore, cellulose-based hydrogels are an environmentally friendly alternative to synthetic materials, which present suitable properties that make them a very attractive option to be used in bioengineering strategies, as well as in drug delivery technologies.

8 Future Perspectives

In future approaches, the challenge is to produce new biomaterials with the ideal characteristics that were mentioned and still fulfill the clinical and industrial requirements. The ideal would be to develop therapeutic materials with a high healing power and, additionally to the total recovery of the damaged skin, are also easy to apply, thus developing an approach with the advantage to produce sustainable and safe cellulose-based hydrogels.

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Cellulose-Based Nanosupports for Enzyme Immobilization

41

Erienne Jackson, Sonali Correa, and Lorena Betancor

Contents

Abstract

Integration of biocatalysts and nanoscale materials offer multiple advantages over micro-scaled heterogeneous biocatalysts. Apart from providing reusability and sustainability of the enzyme, the use of nanosupports is aimed at increasing

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the surface area available for biocatalyst immobilization and improving the yields in bioconversions through better biocatalyst mobility and less diffusional problems. Among many nanomaterials for enzyme immobilization, cellulose stands out as biocompatible, biodegradable, and environmentally-friendly regarding its biological source. In this chapter, we discuss the steady advancement in utilizing different nanostructured cellulosic materials for enzyme immobilization. We address the use of hybrid materials that include cellulose and improve the properties of the heterogeneous biocatalyst. The methodologies for functionalization and integration of enzymes on nanocellulose hydrogels are discussed including covalent linkage through chemical modification, entrapment, and cross-linking. We consider its applications to biomedicine, food industry, and environmental science with a special emphasis on the impact of the enzymatic properties caused after immobilization on cellulosic supports.

Keywords
Enzyme immobilization · Cellulose · Nanosupports · Biocatalysis · Nanobiotechnology

1 Introduction

Nanobiocatalysis is a new frontier of emerging nanosized material supports in enzyme immobilization application. Enzymes are remarkable biocatalysts and have been used in biotechnology for many years because of their interesting characteristics such as substrate and product specificity, ease of preparation, and ability to function under mild conditions with no toxic by-products for more environmentally-friendly conversions.

Enzyme association to insoluble materials, commonly known as enzyme immobilization, provides a number of advantages to the applied use of enzymes: immobilized enzymes can be reused, minimizes costs and time of analysis, facilitates the continuous use of the biocatalyst, and may improve enzyme properties such as operational or thermal stability [1, 2]. A wide variety of techniques are now available for the preparation of immobilized enzymes that may include chemical or physical mechanisms, addition of aiding agents during immobilization, or combination of different strategies to obtain more active and stable preparations. Moreover, investigations on material science have contributed with a plethora of new supports compatible with enzyme activity and better physical and mechanical properties. Such is the case of nanosupports, rapidly adopted for enzyme immobilization, as they reduce diffusion limitations and maximize the functional surface area to increase enzyme loading. Active immobilized enzymes in nanomaterials, also known as nanobiocatalysts, have been studied for a wide variety of applications [3].

Cellulose, as a natural polymer resource is abundant, renewable, and biocompatible and has gained interest due to its optical, mechanical, chemical, and rheological properties that make it suitable for materials applications, actuators/sensors, drug delivery systems, biomedical science, and biotranformations [4]. As it is produced

from plants and bacteria, the nature of its structure varies and offers numerous possibilities for the attachment of enzymatic molecules and functionalization with non-natural reactive groups which further expands the possibility of associating biocatalysts to its structure. It was only in the last 10 years that researchers were able to develop and study strategies for the preparation of cellulose-based nanostructures. These studies have rampaged from a mere 4 articles in 2006 and 2007 related to "nanocellulose" to 365 articles published in 2016 (source Scopus). The recent interest on these materials is not fortuitous but the result of a slow unveiling of the opportunities that this material has on biotechnological applications. It is therefore timely to revise the piled evidence of nanocellulose materials that have been used in the immobilization of enzymes, the different methodological approaches to obtain them and their suitability for biocatalytic applications with a view of the future impact of these composites in biocatalysis.

2 Cellulose Architectures for Enzyme Immobilization

There are a number of cellulose nanostructures able to support enzyme immobilization: cellulose nanofibers (CNF), which can be electrospun, micofibrillated cellulose (MFC), nanocrystalline cellulose (CNC), or bacterial nanocellulose (BC). CNF can be produced from both cellulose I source, such as wood fibers, cotton, and agricultural crops, and cellulose II source, such as lyocell fibers using various techniques such as grinding, high-pressure homogenization, and sonication. There are four different polymorphs of cellulose: cellulose I, II, III, and IV. Cellulose I, native cellulose, is the form found in nature, and it occurs in two allomorphs, Iα and Iβ. Cellulose II, or regenerated cellulose, the most stable crystalline form, emerges after recrystallization or mercerization with aqueous sodium hydroxide. The major distinction between these two forms of cellulose lies in the layout of their atoms: cellulose II has antiparallel packing, whereas the chains in cellulose I run in a parallel direction. Finally, cellulose III_I and III_{II} are obtained by ammonia treatment of cellulose I and II, respectively, and with the modification of cellulose III with glycerol, cellulose IV is finally produced [5].

The isolation of cellulose from its sources can be carried out by top-down or bottom-up method. The bottom-up approach is used to process material from small molecules into complex structures [6]. The top-down method usually involves various mechanical, chemical, and biological treatments, or a combination of two or more methods which is used for the removal of plant constituents apart from cellulose.

2.1 Natural Cellulose Supports for Enzyme Immobilization

Natural sources of cellulose could be generalized as rigid and partially crystalline. Cellulose is the main constituent in the most abundant organic compound on earth, especially within wood and natural fibers (kenaf, palm, cotton, hemp, flax, etc.). Almost 65–70% of cellulose compound is contained in plant fibers and comprised C,

H, and O elements [1, 7, 8]. Kenaf (*Hibiscus cannabinus* L.) is a lignocellulosic fiber having a high cellulose content, low specific gravity, and good mechanical properties along with good chemical characteristics, large surface area, and low coefficient thermal expansion. The isolation process of kenaf raw bast fiber has been done by using combinations of chemical and physical treatments which can remove matrix substances such as lignin and hemicellulose, and disintegrate the micron-sized cellulose fiber into nanofiber [9]. This process results in changes in the appearance of the material from micron-sized to nanosized fibers. It is organized as web-like network structure with long entangled cellulosic filaments with an average diameter ranged as less than 100 nm right up to less than 10 nm depending on the ultrasonication output power. Thus, ultrasonication disintegration plays an important role in the determination of the diameter of the fiber. The nanofibril has been successfully observed as an individual wire-like fiber [10], arranged in longitudinal direction as aggregated fibers with high specific surface area and strong association due to interfiber hydrogen bonding between hydroxyl groups of adjacent fibers.

2.2 Microfibrillated Cellulose

Microfibrillated cellulose (MFC) is a material derived by disintegrating digested cellulose through a homogenizing process in a reciprocating motion producing a high pressure drop. The strategy results in shearing and impact forces that in turn expose microfibrils regardless of the starting material [11]. The production of MFC by fibrillation of cellulose fibers involves intensive mechanical treatment. Additionally, it could involve prior chemical treatments to purify the cellulose depending on the raw material. MFC consists of aggregates of cellulose microfibrils. Its diameter is in the range 20–60 nm and it has a length of several micrometers. If we consider that the microfibrils have a 2–10 –nm-thick fibrous cellulose structure and a length of several tens of microns, then MFC is composed of 10–50 microfibrils [5]. The raw materials and fibrillation techniques dictate the cellulose degree of polymerization, morphology, and nanofiber aspect ratio. MFC can further be subclassified depending on the treatment it undergoes. On transverse cleavage of the microfibrils along the amorphous regions and subsequent sonication, they form rod-like structures called “cellulose whiskers” with a typical diameter of 2–20 nm and wide length distribution of 100–600 nm. Their almost perfect crystalline arrangement makes them a potential reinforcing material [12].

2.3 Cellulose Nanocrystals

Cellulose nanocrystals (CNCs) are rod-like cellulose nanomaterials that can be economically prepared from various cellulosic materials by the elimination of amorphous regions of cellulose. This material is interesting as a nanofiller due to its nanoscale dimensions, high specific area, and highly rigid crystalline structure [11, 13]. Generally, CNCs are formed upon the elimination of disordered or amorphous regions of cellulose through several strategies, including acid hydrolysis,

microfluidization, and TEMPO-mediated oxidation. BC and cotton linter cellulose long fiber (CLC) can also produce cellulose nanocrystals (CNC) [14]. Reports from Roman et al. have shown that CNCs are much safer than other nanomaterials in use in biomedicine as targeted drug delivery systems. They have been used to immobilize various enzymes such as lysozyme, papain, and glucose oxidase [4, 13, 15]. The CNC-CLC and CNC-BC showed higher loading capacity of the protein, enhanced stability and activity, and overall a potential support for application in biomedicine, bioelectronic, and biocatalytic fields.

2.4 Bacterial Cellulose Nanosupports

Cellulose synthesized by bacteria is called bacterial cellulose (BC) or sometimes microbial cellulose and is obtained as a gel-like three-dimensional mat formed by entangled nanofibrils of cellulose [16]. Different from cellulose from wood pulp, BC is devoid of other contaminating polysaccharides which provide high crystallinity and purity to the material and its isolation and purification are relatively simple, not requiring energy- or chemical-intensive processes. The ability to naturally synthesize BC is restricted to a few genre of bacteria being the most common bacteria associated with the synthesis of cellulose *Gluconacetobacter xylinus* as it is the only one able to produce it at the industrial level [17]. After polymerization of glucose residues occurring in the cytoplasm, an extracellular secretion of the glucan chains occurs in a hierarchically linear arrangement favored by van der Waals forces and hydrogen bridges. Intra- and interfiber hydrogen bonding favor crystalline packing of the fiber for amorphous and crystalline regions [18]. The resulting microfibrils aggregate to produce a typical ribbon assembly with a lateral width of 40–60 nm. This structuration provides a specific density, tensile strength, and hydrophilicity that suit the material for functionalization and application to cosmetic industry, paper industry, food processing and packaging, and tissue engineering. Furthermore, the unique fibrillar nanostructure of BC (Fig. 1) determines its distinguished physical and mechanical properties such as high porosity, large surface area, excellent mechanical strength, and good biocompatibility [19]. BC-forming microorganisms can be cultivated in mannitol-based medium with alternative source of carbons and the supernatant freeze-dried to form a BC sponge after purification. Acid hydrolysis of BC form bacterial cellulose nanocrystals (BCNs) that have a higher hydrophilicity due to increased number of hydroxyl groups while being able to establish hydrophobic interactions due to its highly ordered crystalline organization (Fig. 1). This amphiphilic capacities can be applied to stabilize surfactant-free emulsions [20].

2.5 Electrospun Cellulose

Electrospinning is a simple, cost-effective, and scalable technique that utilizes electrical charge to form fine fibers from a polymer solution or polymer melt. In the past decades, electrospinning has emerged as a facile, economical, and scalable

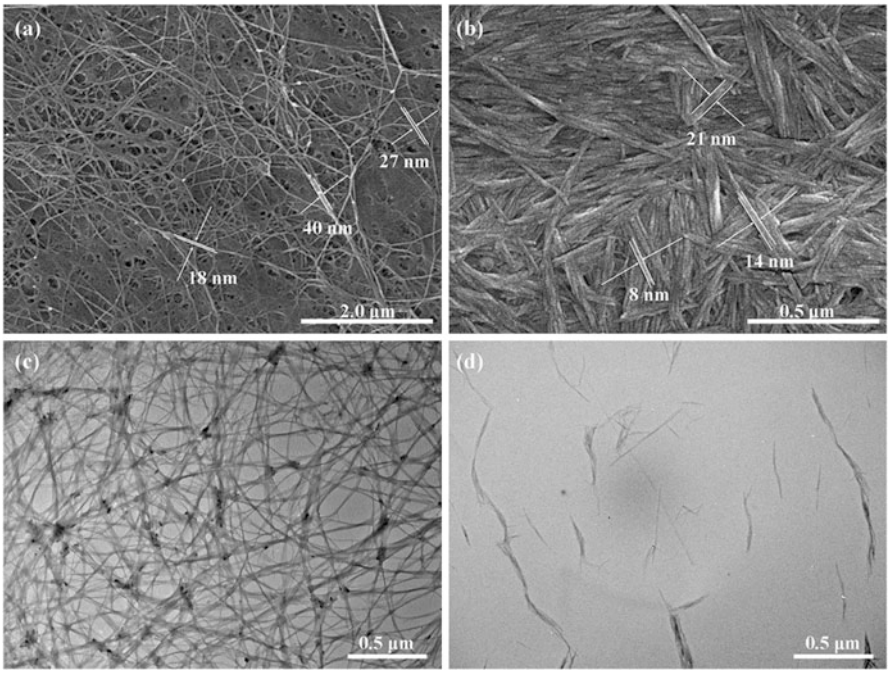

Fig. 1 An example of bacterial cellulose from *Acetobacter xylinum*. SEM images of (**a**) BC and (**b**) BCNs; TEM images of (**c**) BC and (**d**) BCNs. (Reproduced with permission from [20])

technique to produce polymeric fibers with a diameter ranging from micro- to nanometer scale. The biggest advantages of electrospun nanofibers are the high specific surface area, high porosity, and interconnectivity [21]. In biocatalysis, electrospun nanofibers could be used as the support for enzyme immobilization, and the immobilized enzyme could be reused and simultaneous biocatalytic reaction and enzyme-product separation is possible.

Substrates of this technique can be salts of cellulose such as cellulose acetate. The properties of the final material obtained can vary depending on the concentration and electrical conductivity of the starting solution, applied electrical potential, fiber collection distance and time, flow rate, and inner diameter of the reservoir during the process [6].

Electrospun cellulose has been used in a layer-by-layer self-assembled (LBL) configurations based on the electrostatic interactions of additional materials sequentially added to cellulose mats. This material was prepared by alternate adsorption of highly positively charged enzyme Naringinase (NA) and negatively charged alginate (ALG) from dilute solutions on the surface of negatively charged cellulose acetate nanofibrous mats via electrostatic attraction. The self-assembly of NA and ALG gave the reversal of the surface charge, demonstrating the successful polyelectrolyte multilayer deposited onto electrospun cellulose acetate nanofibers [21].

2.6 Synthetic Supports

In the recent years, the preparation of lignocellulose-based materials and biomimetic synthetic wood composites containing cellulose, hemicellulose, and lignin by using ionic liquids (ILs) as well as cellulose/starch/lignin film, lignocellulose aerogel, and all-wood composites have been reported [8, 22]. The major components of wood have been reported to be dissolved in ILs and successfully reconstituted as hydrogels, thin films, and electrospun materials. Fabrication of homogeneous composites from cellulose/hemicellulose/lignin has been achieved via an uncomplicated process by using in 1-ethyl-3-methylimidazolium acetate resulting in hydrogel beads composites with controllable properties [8]. The material shows a regular spherical shape and it is noted that the surface could be controlled by altering the ratio of cellulose, xylan, and lignin. When all three components were present, it was referred to as a wood mimetic composite which was a viable support for the entrapment of lipase and stabilization of its activity.

3 Strategies for the Immobilization of Enzymes in Cellulose-Based Nanocarriers

There are many enzyme immobilization approaches in cellulose-based nanocarriers already available and many more are being developed. Most of these approaches share the goals of finding a biocompatible support for enzyme immobilization, provide a higher surface area to increase the enzyme loading, and achieve high stability and reusability of the biocatalyst with a simple and mild methodology. In this regard, cellulose materials have been studied due to its low cost and biocompatibility [23, 24]. Cellulose materials have been proven to be environmentally-friendly and are able to work under mild conditions [23, 25].

Among many strategies for enzyme immobilization, cellulose-based nanobiocatalysts have been developed mainly using four different approaches to retain the enzyme in the cellulosic support: entrapment, cross-linking, adsorption, and covalent immobilization.

In this chapter, we describe these four immobilization strategies in cellulosic-based nanosupports and examine the impact of the immobilization process on the biocatalyst activity and stability through several examples.

3.1 Immobilization by Cross-Linking

Chemical modification of enzymes after immobilization such as chemical cross-linking is a widely used strategy in the preparation of insoluble biocatalysts [26]. The enzyme is generally adsorbed to the nanosupport and then cross-linked with a bifunctional agent such as glutaraldehyde (Fig. 2). This approach can improve the enzyme stability as well as reduce enzyme leakage, a common problem in

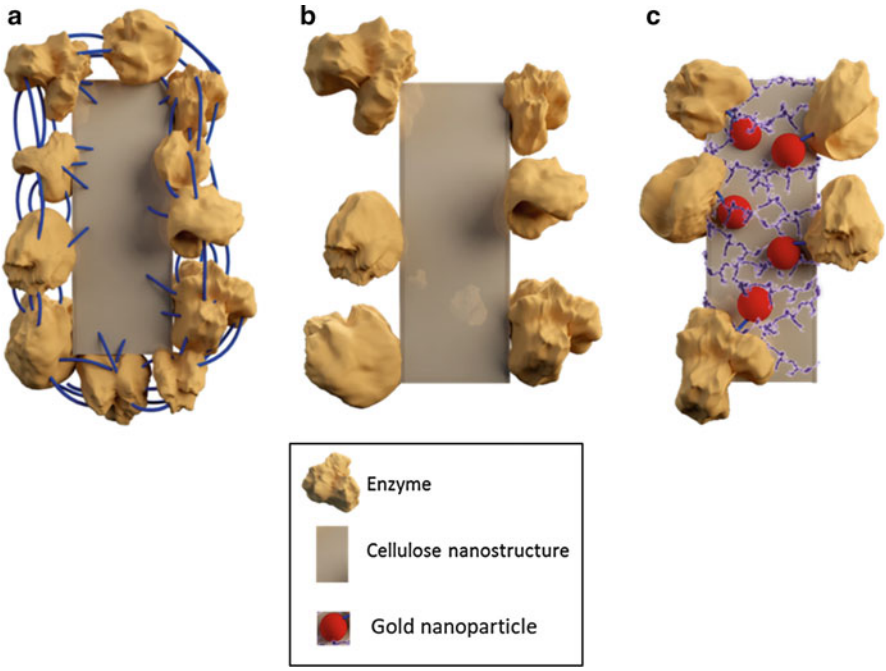

Fig. 2 Schematic representation of an enzyme immobilized on cellulose nanosupport via (**a**) adsorption and cross-linking, (**b**) physical adsorption, and (**c**) covalent immobilization to gold nanoparticles (AuNPs) attached to the support

noncovalently attached enzymes to supports. An alternative approach to a previous adsorption of the enzyme on a support is its precipitation and further cross-linking. Further advantages could be obtained if additives or other material are present during the precipitation. For instance, magnetic nanoparticles can be added to the mixture to form a hybrid nanobiocatalyst to ease its separation from reaction media.

Magnetic cellulose nanocrystals (MCNCs) have been used as a support for enzyme immobilization [13, 27]. The enzyme can be mixed with an aqueous suspension of MCNC and be deposited on its surface in the presence of a precipitant such as ethanol. Upon precipitation, addition of a cross-linking agent such as glutaraldehyde generates a chemical attachment between the immobilized molecules [23].

Immobilization on MCNCs via the described precipitation-cross-linking process was successfully accomplished with different types of enzymes [13, 27]. For instance, following this strategy, a nanobiocatalyst papain/MCNC has been prepared with high enzyme-loading capacity (333 mg protein/g MCNCs). The highest enzyme activity recovery was 80.1% at a mass ratio of 1:3 papain to MCNC. This could be attributable to the abundant active –OH groups of the cellulose nanocrystals that contribute to the cross-linking of the enzymes on the MCNC. When comparing the nanobiocatalyst with the free enzyme, the optimal pH value increased from 6.5 to 7.0 and the temperature for the highest activity was 75 °C, 5 degrees higher

than that of the free enzyme. The change in optimal temperature was attributed to an increase in the enzyme conformational rigidity (seen in a secondary structure study). When comparing the kinetic behavior of free and immobilized papain, a higher V_{max} (2.07×10^{-2} compared to 1.19×10^{-2} μmol/ml.min) and lower K_M (0.85–1.27 mM) were found, thus demonstrating the increase in enzyme-substrate apparent affinity. This phenomenon could be attributable to the fact that the enzyme was anchored on the surface of MCNC, making the substrate accessible to the enzyme and in turn increasing the apparent affinity, or that the immobilization of papain onto the MCNC may have resulted in the conformational changes, helping the enzyme to suitably orient its active site toward the substrate. The immobilized enzyme was also proved to be more thermally stable. When comparing at the same temperature, the immobilized enzyme exhibited higher activity recovery than its free counterpart, 30% after 7 h incubation at 80 °C, while the free enzyme was inactivated after only 3 h. Moreover, the nanobiocatalyst showed no significant loss of activity when stored at 4 °C for 30 days. Finally, the reusability of the immobilized preparation was successful in maintaining 52.4% of its initial activity after 6 cycles.

3.2 Immobilization by Physical Adsorption

Physical adsorption of the enzymes on insoluble cellulose-based nanosupports has been reported elsewhere for the production of stable immobilized preparations that avoided leakage provided a strong enzyme-support interaction was established [28]. This immobilization approach has a major advantage considering the simplicity of the steps required, although functionalization of bare cellulose with ionizable/hydrophobic groups is sometimes necessary to achieve strong enzymatic adsorption of enzymes.

Physical adsorption of enzymes is feasible onto cellulose nanocrystals (CNCs) by incubating both the support and the enzyme under shaking at room temperature [13]. At neutral pH, a high fraction of sulfonate groups on the CNCs are ionized and the cationic sites or amino groups of the enzyme may have ionic interaction with anionic groups of CNCs (Fig. 2). The adsorption level of enzymes onto cellulose increases by the oxidation of cellulose primary hydroxyl groups to carboxyl groups; this strategy has been tested with cellulose fibers and could be translated to nanostructures [29].

When immobilizing a lipase from a *C. rugose* with this approach, an immobilization yield was low (51%) [13]. The decrease of lipase activity after immobilization may be due to the changes in spatial conformation of lipase and lower accessibility of substrate to the active site. However, the thermal stability can be enhanced by this approach. In the case of lipases, an immobilized enzyme to CNCs maintained over 50% of the residual activity when incubated at 60 °C for 1 h. Under the same conditions, the residual activity of the free lipase was only 11%. When comparing the half-lives, the immobilized enzyme was 27 times higher than of the free lipase. This increase in thermal stability may be associated to the enhanced ionic

interactions between anionic sulfonate groups of CNCs and the lipase, and the increased interactions caused by the higher surface area of the nanomaterial [13]. With this strategy, the pH profiles of free and immobilized lipase were similar, pH 8 being the optimal for both. A difference was found at pH 5, where the relative activity of immobilized lipase was 3.7 times higher than that of free lipase, and at pH 10, where free lipase showed no activity while the relative activity of immobilized lipase was 27.8%. The pH profiles for the stability of free and immobilized lipase were also very similar after a 5h incubation. The residual activities of immobilized lipase in buffers from pH 3 to pH 8 were approximately 140% higher than those of the free lipase. At alkaline pH, the stability of the lipase was significantly enhanced by immobilization on CNC (8.8 times higher at pH 10). Increased activity and stability in alkaline pH may be caused by increased ionic interaction between anionic groups of CNCs and the lipase since the anionic form of the sulfate half-ester in CNC is dominant at an alkaline pH.

Physical adsorption of lipase not always results in a more stable preparation. In a study where the adsorption of a *Candida rugosa* lipase was performed on a cellulose nanofiber membrane, the preparation demonstrated a low enzyme loading and poor enzyme stability [30]. These types of examples still prove the necessity of protocol optimization in order to tailor the immobilization strategy to a particular support or a desired enzyme.

Functionalization of nanocellulose-based supports for adsorption of enzymes has also been achieved via coverage of the cellulose surface with ionic polymers. Efficient immobilization of papain was achieved using CNCs associated to polyethyleneimine (PEI) modified Fe_3O_4 nanoparticles [16]. Magnetic nanoparticles embedded on CNCs facilitated the separation of the particles from a reaction mixture, simplifying the reuse of the biocatalysts. This support was successfully used for the immobilization and separation of papain from the reaction mixture which under optimal conditions resulted in a preparation with an enzyme activity of 227 μg/min.g. When studying the kinetic parameters of this preparation, the immobilized papain required higher substrate concentration compared to the free papain which could be explained by the increased steric hindrance and diffusion impediments. However, compared with free papain, the immobilized papain still demonstrated high catalytic efficiency.

Also, the immobilized papain exhibited higher relative activity in both acidic and alkaline pH ranges when compared to its free form. The immobilized enzyme retained over 90% of its original activity after incubation for 1 h at 40 °C, almost twice the activity measured for the free enzyme [16].

3.3 Covalent Immobilization

Covalent immobilization of enzymes is often chosen over adsorption strategies because it overcomes the primary disadvantage of adsorption which is enzyme dissociation (leakage) [28]. A number of functionalization strategies have been developed for cellulose nanomaterials for the covalent bonding of enzymes

[13, 31, 32]. One of this approaches involved functionalization of cellulose nanocrystals (CNCs) with cyanogen bromide, a functional group that is able to react with amino-terminal groups of enzymes under neutral pH [31]. Peroxidase has been immobilized in CNCs following this approach resulting in a highly active preparation (594 IU/g) with a higher catalytic efficiency when compared to the free enzyme.

Modification of CNCs can be also obtained via esterification with amino acids such as glycine through the abundant hydroxyl groups on the CNC surface. Lysozyme, for example, can be covalently immobilized via amide linkage of its glutamate and aspartate residues to the surfaces of amino-modified materials. In this case, lysozyme-amino-glycine-CNC conjugates were created using a carbodiimide-activated coupling reaction. The prepared nanobiocatalyst showed a high enzyme loading (604 mg/g CNCs) and high antimicrobial activity (1500 IU/mg biocatalyst) against *Micrococcus lysodeikticus* [32].

An alternative strategy for covalent immobilization can involve the addition of another material to the system. An approach described by Boluk et al. [33] involved the immobilization of a glucose oxidase (GOx) through the formation of covalent bonds between the enzyme and gold nanoparticles (AuNPs) attached to rod-like cellulose nanocrystals (Fig. 2). The AuNPs must be previously functionalized with thiol linkers and later activated, offering a multipoint attachment of GOx molecules to the nanocomposite surface. In this approach, the CNCs have been incubated with cationic PEI which covers the nanocrystals by ionic interactions; then negatively charged AuNPs were deposited on the CNC/PEI electrostatically resulting in a CNC/PEI/AuNPs nanocomposite. The enzyme (GOx) was covalently attached to the thiol-functionalized nanocomposite by activation of the –COOH group using 1-ethyl-3-(-3-dimethylaminopropyl) carbodiimide hydrochloride (EDC) and N-hydroxysuccinimide (NHS). The best case resulted in a 25.2 mg of GOx loaded per gram of support. Interestingly, the amount of GOx immobilized on this support increased with decreasing thiol–linker length. The difference could be attributed to their ability to access the AuNPs, as these particles are densely packed.

3.4 Combined Strategies

A new trend in the preparation of immobilized nanobiocatalysts is the combination of different strategies previous to, during, and/or after the immobilization process. The different strategies may have a synergistic effect on the desired properties of the final enzymatic preparation. To improve both loading and stability of enzymes, a three-step approach of enzyme precipitate coating (EPC), consisting of covalent enzyme attachment, enzyme precipitation, and crosslinking, has been successful in achieving both high enzyme loading and stability of enzymes on cellulose nanofibers (CNFs) (Fig. 3a) [34]. Such is the case of immobilization of α-chymotrypsin (CT) on CNFs by the EPC approach. In this approach, magnetic nanoparticles can be added to the enzyme mixture during the precipitation and cross-linking steps to produce

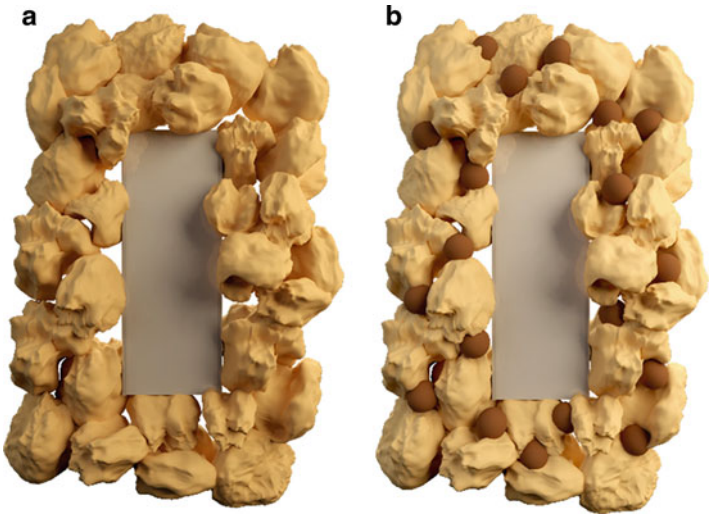

Fig. 3 Schematic representation of enzymes immobilized to cellulose nanofibers by (**a**) enzyme precipitate coating (EPC) and (**b**) magnetically separable EPC (Mag-EPC)

magnetically separable EPC (Mag-EPC) allowing for facile nanobiocatalyst separation (Fig. 3b).

As previously mentioned, this immobilization process consists of three steps. First, carboxyl groups of CNFs can be modified by EDC/NHS reaction for the covalent attachment between enzymes and CNFs, second, enzyme precipitation by ammonium sulfate, and third, enzyme cross-linking with glutaraldehyde treatment. The amine-functionalized magnetic nanoparticles can be added to enzyme solution in the step of enzyme precipitation (Fig. 3b).

The enzyme loadings with (Mag-EPC) and without (EPC) magnetic nanoparticles were estimated to be 3.5 and 3.0 mg CT/mg CNF, respectively. Interestingly, Mag-EPC showed two times higher activity than EPC. The efficiency of cross-linking between enzymes and magnetic nanoparticles was improved possibly due to a higher amount of amine groups on the surface of magnetic nanoparticles, resulting in an increased enzyme loading of Mag-EPC than EPC, as reflected in the activity data (0.43 and 0.74 IU/mg CT for EPC and Mag-EPC, respectively). After incubation under rigorous shaking for 30 days, EPC and Mag-EPC maintained 77% and 50% of their initial activities, respectively, while the free enzyme showed only 0.2%. High stability of EPC can be explained by ammonium sulfate precipitation and cross-linking of CTs. Enzyme precipitation by ammonium sulfate allows enzyme molecules to be closely packed based on “salting out” effect. Interestingly, the Mag-EPC residual activity was lower than that of EPC; this could be caused by the release of large aggregates of CTs and magnetic nanoparticles which would make the enzyme more vulnerable to denaturation under rigorous shaking [34].

3.5 Immobilization by Entrapment

Immobilization by entrapment involves the physical confinement of one or more enzymes in an insoluble matrix. In this strategy, the matrix is usually formed during the immobilization process. The bibliography related to immobilization by entrapment in cellulose nanosupports is scarce. The main drawback for this approach could be related to the very low solubility of cellulose in an aqueous solution since is highly crystalline. Nonetheless, there are successful cases using micro-sized supports. For example, a lipase from *C. rugose* was entrapped in a hydroxypropyl-methyl-cellulose and chitosan matrix. Although this strategy involved many steps and over 48 h of synthesis, the result was a highly active and stable preparation [35].

Also, the rapid development of more and greener ionic liquids, which can dissolve cellulose, opens a new window of opportunities in this field. Again, successful examples can be found with cellulose-based micro-supports. Lipase from a *C. rugose* was entrapped into a cellulose–biopolymer using a biocompatible ionic liquid, 1-ethyl-3-methylimidazolium. This strategy also resulted in a preparation with good residual activity [36].

The technological approach employed on these successful cases could be applied for the development of similar strategies involving nanocellulose.

4 Cellulose-Based Nanobicatalysts at Work

Application of immobilized enzymes on cellulose spans a wide variety of fields. The biodegradability of cellulosic materials has recently drawn the attention of researchers which boosted investigation of its potential in sensitive biotechnological areas such as biomedicine or environmental sciences. In this section, a few recent examples of cellulose-based nanobiocatalysts will be described to provide the reader with a sense of the applicability of these materials.

4.1 Biomedical Applications

Reactive oxygen species are implicated in cellular injures, the initiation and progression of the aging process, and a vast variety of clinical abnormalities. In order to reduce the damage generated by these compounds, a nanofibrous cellulose mat containing attached catalase was prepared and tested in vitro on human umbilical vascular endothelial cells (HUVECs). The immobilized preparation based on electrospun nanofibers proved to have a protective effect on cells previously exposed to H_2O_2 which in turn pointed to a potential strategy to prevent cell damage by reactive oxygen species. The work also showed that the number of coating bilayers in the catalase-modified nanofibrous mats acted as important factor affecting their cytotoxicity and biocompatibility. This was an explorative work with potential to overcome H_2O_2-induced adverse effects at the cellular levels [37].

The antibacterial properties of lysozyme, a hydrolytic enzyme that catalyzes the breakdown of peptidoglycan polymers found in the bacterial cell wall, has been exploited and tested while using immobilized preparations on cellulosic materials. In comparison to many other antibacterial nanoparticles in use, lysozyme immobilized on cellulose possesses low toxicity, high biocompatibility, and selectivity. Researching its potential in a biomedical wound dressing, lysozyme was immobilized via different approaches to cellulose nanofibers aerogels (CNFs) [38]. The performance of the nanobiocatalysts was evaluated against nonimmobilized enzyme and silver nanoparticles. The antimicrobial activity of the preparations was tested against *Escherichia coli* and *Staphylococcus aureus* demonstrating the feasibility of using lysozyme-modified CNFs for this application. The preparation containing lysozyme was not only inhibitory of bacterial growth but was also more stable than the soluble enzyme, which amplifies the possibilities of its application considering the importance of shelf life of biological based products.

A work from Abouhmad et al. [39] also investigated the antibacterial properties of a lysozyme immobilized on CNC. Following different approaches for the integration of hen egg white- and T4 lysozyme, the work demonstrated that the surface modification and the mode of immobilization are critical for the retention of the enzymatic (lytic and hydrolytic) and antibacterial activity as well as stability of the immobilized enzymes. The positive charge on the nanocrystals and lysozyme activity improved the enzymatic action and broadened the scope to Gram-negative bacteria that are normally more challenging to inactivate.

Biosensors offer simple, portable, and disposable analytical devices applicable in clinical diagnosis, food quality control, and environmental monitoring. They depend on a biological recognition capable of being translated on a signal proportional to a target analyte. Particularly, paper-based sensors that offer affordability and ease of preparation although protein immobilization could be challenging to achieve an even distribution of oriented enzyme molecules that could increase the sensibility of the sensing device. A recent work on the development of a lactate biosensor has tackled this problem by using a recombinant lactate dehydrogenase fused with a cellulose-binding domain (CBD) which in nature promotes arbohydrate binding functionality for cellulases. The tag allowed a highly specific binding affinity on filter paper. Moreover, it enhanced enzyme binding capacity and stability, leading to much improved sensor sensitivity and lifetime. The one-step binding procedure using enzyme crude extract aimed at an efficient sensor fabrication strategy for production of high-performance paper sensors that could be extended to nanocellulosic materials for increased sensibility [40].

In another biosensing approach, glutamate dehydrogenase was immobilized on bacterial cellulosic nanofiber with a view on its application in artificial kidney machines and their dialysate liquid regeneration systems as a glutamate-sensing device. The study showed the success of cross-linked immobilization of glutamate dehydrogenase on 30–70 nm bacterial cellulosic nanofiber from *Gluconacetobacter xylinum*. The enzyme was cross-linked to the nanofibers using glutaraldehyde. The study provided an inexpensive, simple, efficient, and reliable technique for

immobilization of glutamate dehydrogenase on bacterial nanofiber which may contribute to find alternative for glutamate determination in solution [41].

4.2 Food Applications

Stem bromelain is a cysteine protease obtained from stems of pineapples (*Ananas comosus*). Although it finds some applications in medicine, this protease is widely used in food industries such as beer clarification, meat tenderization, and baking industries. Using casein as a model substrate, Talingtaisong et al. demonstrated that when the enzyme was immobilized on gauze-reinforced regenerated cellulose (RC) fibers, it became more heat resistant [42]. The enzyme was attached to the RC fibers through covalent immobilization via aldehyde groups introduced by activation with glutaraldehyde and was able to resist up to nine reuses in casein hydrolysis with 40% loss in activity. The results provide an opportunity for bromelain to be reused and used in other processing conditions.

Another interesting application of a cellulose-immobilized biocatalyst is that of naringinase. Narinign and limonin are two of the major compounds that contribute to a bitter taste in citrus juices. Enzymatic and physicochemical treatments have been applied to reduce bitterness, naringinase being one of the enzymes applied as it is able to break down naringin in flavorless products. Naringinase was immobilized within a hybrid layer-by-layer self-assembled material containing alginate and electrospun cellulose acetate nanofibers [21]. As expected, the activity of immobilize naringinase increased with multilayer increasing. The immobilized preparation was applied to remove the bitterness in the grapefruit juice. About 22.72% naringin and 60.71% limonin were removed from the grapefruit juice by adsorption and hydrolysis. The results demonstrated that naringinase-immobilized electrospun cellulose acetate nanofibrous mat are potential materials to remove bitterness for fruit juice.

4.3 Environmental Applications

Biobased treatments of contaminant compounds have received a great deal of interest due to their minimal impact on the ecosystem, their higher efficiency, and their cost effectiveness. Application of immobilized decontaminant biocatalysts is one of the approaches followed to treat, sense, or remove contaminant wastes from water and soil. Although the literature on cellulose-immobilized enzymes on decontamination is not abundant, a few recent examples have demonstrated the potential of cellulosic-supported enzymes for this application. For example, laccase, a well-known phenol/polyphenol decontaminant biocatalyst, was immobilized on cellulose nanofiber and utilized for reactive dyes and simulated dye effluent (SDE) decoloration [43]. After covalent immobilization on electrospun nanofibers, the immobilized preparation was able to decolorate solutions of six different reactive dyes. Optimization of the conversion was performed after statistical analysis revealing that both the concentration of immobilized enzyme and type of

mediator for the catalysis were determinant in the result of the decontamination reactions. The immobilized preparations could be recycled more than 10 times while maintaining more than 50% of its initial activity.

Another example that represents a promising application of immobilized enzymes in cellulosic materials is the utilization of an ether hydrolase enzyme for the decontamination of 2,4-dinitroanisole (DNAN) [44]. This compound is nowadays preferred to 2,4,6-trinitrotoluene (TNT) given that it is less heat and shock sensitive. Strategies to decontaminate firing ranges and wastes from manufacturing sites should comply with biosafety and environmental regulations and therefore there is a constant search for new strategies to remediate explosive components. Additionally, analytical devices for the evaluation of contamination levels are also needed. The work described by the group of Prof. J C Spain used a DNAN demethylase entrapped in biomimetic silica which was further attached to cellulose discs. The immobilized enzyme became more stable and was able to detect 15–500 μM DNAN concentration.

5 Conclusion

Ideal supports for enzyme immobilization should be biocompatible, easy to functionalize, inexpensive, and biodegradable. Additionally, immobilization strategies should provide advantages for enzyme applications over the use of soluble enzymes to counterbalance any additional cost in the preparation of the biocatalyst (i.e., stabilization, increased activity, possibility of reuse). We believe this chapter compiles evidence that proves the benefits of nanocellulosic materials as supports for enzyme immobilization. Moreover, the methodologies for enzyme immobilization on cellulose-based nanocarriers presented suggest that cellulose can be a viable and dynamic material for stable and efficient enzyme immobilization via different approaches. Finally, the variety of applications, which are now in a continuous growth phase, only serve to foretell a promising future for the development of technological solutions involving cellulose-immobilized nanobiocatalysts.

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Bacterial Cellulose-Based Hydrogels: Synthesis, Properties, and Applications

42

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Contents

Abstract

There is an importunate effort taking place worldwide to obtain the innovative hydrogels either from natural, synthetic, or mixed type polymers, ever since the breakthrough invention of the first hydrogel of polyhydroxy ethyl methacrylate. Predominantly the cellulose-based hydrogels attracted the attention of researchers due to its renewable, biodegradable biopolymeric nature. In comparison to plant cellulose (PC), the bacterial cellulose (BC) has been preferred due to its pure fibrous biomaterial nature, high crystallinity, ultrafine three-dimensional nano-structure network, high water absorption, superior mechanical properties,

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biocompatibility, and biodegradability. These promising valuable properties of BC exploit its use especially in hydrogel form in a variety of technological fields like a development of new bacterial cellulose-based hydrogels. The present review focused on its current synthesis methods and use in biomedicine, pharmaceutical, environment, agriculture, etc. In recent years BC itself and in combination have become the subject of intensive studies for the synthesis of hydrogels in search of properties and applications of BC-based hydrogels. On the whole, the review after introducing BC production and its properties discusses the synthesis of BC-based smart hydrogels with various composite materials, formation mechanism, and improved characters. The latest use of BC-based hydrogels in both well-established and innovative high-tech fields is emphatically reviewed. The review concludes with the need for future research with some suggestions for BC-based hydrogels to be commercialized as a smart biomaterial.

Keywords
Biopolymer · Microbial cellulose · Biomaterial · Biocompatible · Biodegradable

1 Introduction

According to Dorothy Jordan Lloyd, hydrogels are "the colloidal condition like a gel which is easy to recognize than to define" or in other words "if it looks Jello, it must be a gel" [1]. The hydrogel material executes like a liquid as well as in another manner like a solid. Hydrogels are considered as water-insoluble, cross-linked, three-dimensional networks of polymer chains plus water that fills the voids between polymer chains. The cross-linking present in hydrogel builds the water-insoluble nature which generates the physical integrity and mechanical strength. The high water-holding capacity of hydrogel implies that the polymer is having a hydrophilic property. The most common classification of hydrogels is based on the type of cross-links and its physical or chemical nature. Another basis for classification is the starting point of synthesis, i.e., production from a monomer or polymer [2]. Further, the classification could be on the basis of polymer source, artificial or natural. The basis of classification may also include physical structure, a method of preparation, ionic charges, and the basis of stimuli [2–4]. Among these, polymer hydrogels are three-dimensional networks of expansively swollen water molecules [5]. Polysaccharide-based hydrogels are immensely important among the polymer hydrogel based on its vast variety of chemical structure and functional potential [6, 7]. Polysaccharides are naturally abundant and expediently available from natural renewable resources like plants, algae, and microorganisms. The diverse compositional and structural features of polysaccharides signify it as easy producible and flexible for gel formation, in comparison with synthetic polymers [8]. The hydrophilic polymer gel is a "solid-like solution" of polymer and water resulted in the equilibrium, and the amount of water retained by the network of the hydrogel

depends on the structure of the polymer network itself and on the environmental conditions, such as the temperature, pH, and ionic strength of the water solution in contact with the polymer [9].The first hydrogel was developed by Otto Wichterle in the 1950s based on poly(hydroxyethyl methacrylate) (PHEMA) which was patented for contact lenses' use; later on, various synthetic, natural, and hybrid polymers were exploited for hydrogel synthesis based on swelling properties, biocompatibility, and bioactivity [3]. Hydrogels have great prospective owing to its ability to absorb a large amount of water or biological fluid and high porosity in addition to soft consistency. Hydrogels are also worked as reversible gels with entanglements, such as ionic, H-bonding, or hydrophobic forces which play a key role in forming the network [10, 11]. Generally, hydrogels are widely used in biomedical field due to their remarkable properties such as high water content, elasticity, biocompatibility, nontoxicity, etc. Swelling behavior of hydrogels plays an essential role in biomedical applications and is mainly related to the network elasticity, the presence of hydrophilic groups (-OH, -COOH, $-CONH_2$, $-SO_3H$) in polymer chains, the extent of cross-linking, and porosity of the polymer [12]. Swelling kinetic is a very significant property for hydrogel applications such as in wound dressings; a fast and large water uptake capacity to absorb the wound exudates is needed [13]. Superabsorbent hydrogels are hydrophilic networks with a high capacity of water uptake, which can absorb, swell, and retain aqueous solutions up to hundreds of times their own weight (dry sample) [14–16].

Hydrogels can be produced from the combination of synthetic–synthetic or synthetic–natural polymers. Recently, many researchers have focused on producing hydrogels from natural polymers due to their less toxicity, biocompatibility, and biodegradability with acceptable mechanical strength. Therefore the fabrications of naturally based hydrogels have emerged involving the use of natural polymers such as starch, cellulose, chitin, gelatin, hyaluronic acid, and much more [17].

The natural polymers either proteins or polysaccharides have many advantages as a hydrogel. Cellulose is such the most abundant natural polymer of glucose monomers which is generally present as a major component of plants and natural fibers such as cotton. Cellulose is a carbohydrate homopolymer consisting of β-D-glucopyranose units joint together by β-1,4-glycosidic linkage [18]. Cellulose fibrils are highly insoluble and inelastic. Their molecular configuration making the tensile strength of cellulose comparable to that of steel and this unique feature provides mechanical support to the tissues which it resides [19]. The microbial synthesis of cellulose is also possible by some Gram-negative bacteria like *Acetobacter xylinum*. Bacterial cellulose (BC) (also known as microbial cellulose, MC) is a potential natural polymer synthesized by bacteria and due to its unique structural and mechanical properties, as compared with higher plant cellulose (PC); BC is expected to become an attractive material for use [20]. This chapter is focused on the production of BC and its properties, synthesis of BC hydrogels with various composites with a mechanism of formation, and applications to use as a biomaterial in new fields.

2 Production of BC and Properties

Interest in BC has grown rapidly in the past decade based on an increase in a number of publications [20]. The structural role of BC protects the bacteria in a natural location, for example, in *A. xylinum* and *Sarcina ventriculi*, or it also works for cell attachment necessary for beneficial association or defensive interaction, for example, in *Rhizobium* and *Agrobacterium* [21]. BC is produced by various species of bacteria, such as *Gluconacetobacter* (formerly *Acetobacter*), *Aerobacter*, *Salmonella*, *Achromobacter*, *Rhizobium*, *Agrobacterium*, *Azotobacter*, and *Sarcina* [22]. *A. xylinum* [23], *A. hansenii* [24], and *A. pasteurianus* [25] are the most potent BC producers. BC is produced traditionally by either static or shaking culture methods. Static culture method has a limitation of a long period with more space, manpower requirement resulting less BC production. On the other hand, agitated culture method gives higher production in less time but converts BC-producing strains into cellulose-negative mutants, which become more enriched than the wild-type strain because of their rapid growth, thereby lowering the productivity of BC [26]. The strategy for BC production has been shown in graphical form in Fig. 1.

The culture method effects on cellulose fiber morphology and structural characteristics and mainly the BC production. Morphological differences between the cellulose produced by static and agitated cultures contribute to varying degrees of crystallinity, different crystalline size, and cellulose content [27]. BC biosynthesis yields nanosized fibers, which are about two orders of magnitude smaller than plant cellulose (PC) fibers. BC shows a peculiar, ultrafine fiber network with high water-holding capacity and superior tensile strength compared to PC [28].

Microfibrillar structure of BC is responsible for most of its properties such as high tensile strength, high crystallinity index, and a higher degree of polymerization.

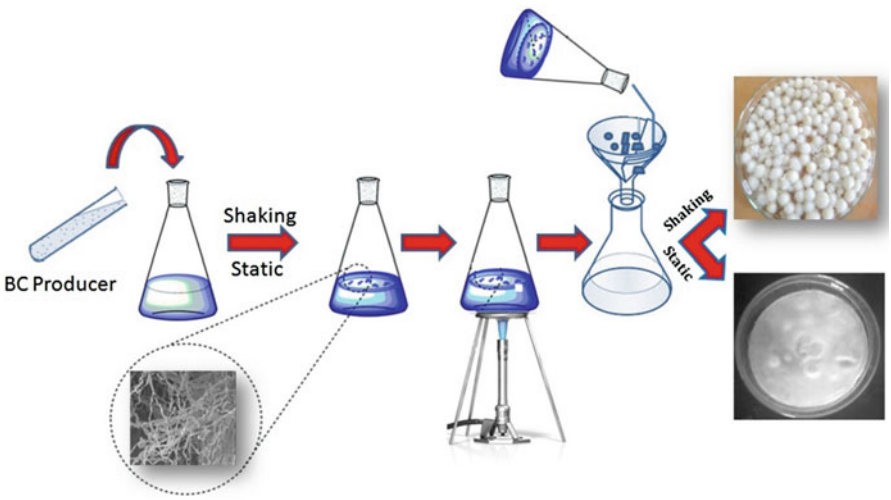

Fig. 1 Schematic representation of strategy for bacterial cellulose production

The BC (0.8%) hydrogel itself has been confirmed for its biocompatible nature and induction of tissue remodeling [29].The chemical composition of its physical properties does not induce an immune response, featuring a promising material with an extensive range of applications in the biological sciences [30]. Bacterial cellulose also exhibits other attractive features, such as a high degree of crystallinity (89%) [31], a high degree of polymerization (14400) [32], and a high specific surface area (37 m^2/g) [33]. Moreover, bacterial cellulose also offers a large surface area, high aspect ratio, and low bulk density, as well as hydrophilicity.

Due to specific properties such as the three-dimensional nanomeric structures, unique physical, mechanical, and thermal properties together with its higher purity BC have been commercialized as high-end products like health, food, high strength papers, audio speakers, filtration membranes, wound dressing materials, artificial skin, artificial blood vessels, other biomedical devices, etc. [34–37].

3 Synthesis of BC Hydrogel Sole and with Various Composite

Day by day there is a gradual decrease in fossil fuel, and hence interest has been increased in biological resources like biomaterial. BC is such renewable, biodegradable biopolymer produced from bacteria. BC has extraordinary properties like high elasticity, porosity, high water-holding capacity, etc. that makes it an interesting candidate for hydrogel formation. In hydrogel formation for application in various fields like biomedicine, drug delivery required the production of customized polymer to provide the functionalized properties. Hence the blending of BC with various natural or synthetic molecules can result into a modified polymer with improved properties. In recent time, there is increased attention in a synthesis of BC hydrogel by combination with another composite in order to improve the properties of the resulting material.

The improvement in BC properties could be made by composite preparation. With this perspective, BC was mixed with different substances like poly(vinyl alcohol) [38, 39], gelatin [40, 41], chitosan [42], starch [43], alginate [44, 45], and acrylic acid [46, 47]. BC-based composites were explored for various biomedical applications such as tissue engineering, scaffold, graft, wound healing coating, synthetic skin, and drug delivery [48–50] with some uses in agriculture and environment.

The first hydrogel reported was by using poly(2-hydroxyethyl methacrylate) (PHEMA). This was the water-insoluble polymer of PHEMA, it can cross-link with water-insoluble BC nanofiber, and this nanocomposite was produced by free radical polymerization of HEMA monomer in the presence of BC in the presence of ultrasound, initiator, and the monomers. This transparent disclosed polymer nanocomposite hydrogel and compositions pertaining to hydrogel applications, particularly contact lenses and optic components for biosensor [51].The electrically conducting composites of BC with aniline monomers (ANI) were prepared [52]. The resultant material BC with poly(aniline) (BC/PANI) showed high electrical conductivity values (0.9 S/cm) and good mechanical properties (40 MPa). Higher

conductivity, improved absorption properties, and a uniform, smooth coating is obtained in membranes prepared with $FeCl_3$ [53, 54]. BC and poly(aniline) (PANI) composites were successfully synthesized by in situ polymerization of aniline by ammonium persulfate (APS) in the presence and absence of gold nanoparticles. The surface roughness is higher in composites, and the polymers interact with each other by strong hydrogen bonds, providing high thermal stability in the BC/PANI composite. The electrical conductivity of composites is highly influenced by the APS in the polymerization step [55].

BC was used as a septum to separate the toluene/aniline solution with an aqueous oxidant acidic solution, and the aniline was polymerized in situ on the surface of the BC. Because toluene disperses aniline and controls the migration rate of aniline toward the aqueous oxidant acidic solution through BC, it can limit the oxidative polymerization to a single side of an interface between the aqueous oxidant acidic solution and BC. The BC component in the new BC/PANI composite can absorb the electrolyte solution and change to a multilayer composite of electrode/electrolyte septum material that could be used in supercapacitors [56].

The nanostructured wet BC as a novel hydrogel was developed as bioanode for microbial fuel cells (MFCs) in which in situ synthesis of polypyrrole (PPYR) was subsequently performed on the BC fibers to generate the novel bioanodes [57]. The phosphorylated BC (PBC) was developed for adsorption of proteins which has larger specific surface area. The phosphorylation increased the adsorption capacity BC for the protein and hence proves as an attractive option for adsorption of proteins [58]. The BC combines with gelatin (G) forming three-dimensional polymeric networks for absorption and retention of huge quantity of biological fluid. The swelling behavior of BC–G hydrogels was affected by gelatin concentration, coating layer, and pH. The swelling mechanism followed the pseudo-Fickian diffusion kinetics [13]. The regenerated BC–gelatin (rBC–G) scaffolds of very porous and biocompatible nature were fabricated for tissue engineering applications. The composite solution of BC–G forms the scaffolds by casting and leaching process. High porosity and rapid swelling of the scaffolds ensure their nutrient exchange ability during practical applications. The enhanced expression of metalloproteases (MMPs) showed that prolonged cell incubation can lead to extracellular matrix (ECM) production inside the three-dimensional (rBC–G) scaffolds. These results demonstrated that 3D rBC–G composite scaffolds are candidates for future biomedical applications, including tissue regeneration [59, 60]. BC nanofibers were shown to be excellent reinforcement agents for the production of starch-based bionanocomposites before and after treatment with *Trichoderma reesei* endoglucanases. The mechanical and thermal properties of BC nanofibers were improved [43, 61]. Nanomaterials of BC could be developed by an innovative method of introducing a different phase (starch) into a cellulose nanofiber network during its assembly [62].

The interesting properties of carboxymethyl cellulose (CMC) and polyvinylpyrrolidone (PVP) lead to the development of different hydrogels by blending with the BC. The BC–CMC and BC–PVP hydrogels prepared by heat treatment are porous enough with viscoelastic behavior which could be utilized

for drug loading and controlled drug release and in soft tissue replacement, respectively [63].

BC–polyacrylamide (PAAm) hydrogels have been proven to possess a uniaxial anisotropy of micron structure with a characteristic size of 11.5 ± 5 μm, the axis being normal to the BC growth surface as revealed by study of spin-echo small-angle neutron scattering (SESANS) [64]. Bacterial cellulose–polyacrylamide (BC–PAA) composite hydrogels are prepared by free radical polymerization in which polyacrylamide (PAA) was introduced into the network of matrices for superb mechanical properties [65].

The acrylamide/BC (AAm/BC) copolymer was developed with irradiation using cobalt 60 gamma source [66]. The epichlorohydrin and *N*,*N*′-methylene bisacrylamide were used as cross-linker for network hydrogel of solubilized BC and acrylamide (Am) by freezing, microwave irradiation, and a combination of both. The release kinetics of hydrogels follows the non-Fickian diffusion mechanism [67]. Hydrogels were synthesized by graft copolymerization of the poly(acrylic acid-co-acrylamide) monomers onto BC fibers by using a microwave irradiation technique. The hydrogels showed lesser release in the simulated gastric fluid than intestinal fluid, suggesting that hydrogels may be suitable drug carriers for oral controlled release of drug delivery in the lower gastrointestinal tract [68]. BC/acrylic acid hydrogel synthesized with electron beam irradiation speeds up the burn wound healing as confirmed in an animal model. Hydrogel encourages faster wound healing by enhanced epithelialization and accelerated fibroblast proliferation. Therefore BC/AA hydrogels are the potential candidate for burn wound dressing material [68]. Hydroxyapatite (HAp)-coated BC scaffold was developed which shows new bone formation derived from existing bone and hence can be used as an effective tool for bone tissue regeneration [69]. Multicomponent BC–gelatin/hydroxyapatite double network composite was synthesized, which combined the advantages of BC/HAp and BC-G and could be used as ideal bone scaffold platform or biomedical membrane in the future [70]. Conducting polymer has been developed by depositing conducting polymer (CP) on BC surface resulting into a double network of BC–CP hydrogels which show integrate electroactivity with biocompatibility which provides a biology–device interface for implantable device production to be used in personalized and regenerative medicine [71].

The nanocrystalline cellulose (NCC) and a water-soluble polymer form a NCC hydrogel in water. The NCC hydrogel can be used to treat or coat devices, for instance, a catheter, whereby the NCC hydrogel inhibits bacterial adhesion to the catheter surface to inhibit biofilm formation and growth of bacteria [72]. A novel copolymer of polylactide and glycidyl methacrylate (PLA-co-PGMA) was prepared and used to modify the BC surface. PLA-co-PGMA was efficient at modifying the surface of BC nanofibrils and improving the compatibility of PLA/cellulose composites [73]. Moreover, polylactide-graft-methacryloxypropyltrimethoxysilane (PLA-g-MPS) was prepared by grafting MPS onto PLA and then used to modify BC [74]. The modified BC possessed a much more hydrophobic nature than virgin BC. Most of the hydrogels lack the mechanical toughness, and hence only limited applications are possible. Hence the double network (DN) structure hydrophilic

polymer was developed which despite containing a high amount of water (90%) had an elastic modulus of 0.4–0.9 MPa [75]. A double network is composed of a combination of a stiff, brittle first network (BC) and soft, ductile second network (gelatin), and hence the DN is formed by a combination of BC–gelatin DN gel [76]. When the BC was combined with sodium alginate/L-carrageenan, there is an improvement in mechanical strength like elastic modulus which could be used for synthetic connective tissues like articular cartilage, semilunar cartilage, tendons, and ligaments [75, 76]. BC and hyaluronic acid (HA) have been prepared and have mainly found applications in biomedical and tissue engineering scaffold materials [77]. The biocompatibility of BC and the importance of hyaluronic acid as a component of extracellular matrix qualify the polymeric composites as promising biomaterials for tissue engineering [78, 79]. The BC–HA hybrid membranes can be produced in in situ conditions during the production of BC, suggesting the interaction of HA with BC microfibrils causing changes in the membrane characteristics [77].

A new wound dressing based on BC/collagen (BC/COL) hydrogel has been proposed for wound healing. The BC/COL hydrogel found better for wound healing than collagenase hence proves as a potential candidate for skin regeneration wound dressing [80]. BC–vaccarin (BC–Vac) membranes were successfully produced on large scale for wound dressing materials. Addition of drug vaccarin into the BC membranes increased the malleability indicated by the increment in elongation at break compared with BC. BC–Vac had no cytotoxicity, and wounds treated with BC–Vac has epithelialized and regenerated faster than treated with BC and hence could be a good carrier for cell growth [81].

The reduction of brittleness of polyester (PO) by using reinforcement leads to the development of BC nanofibers–polyester composites. The modulus elasticity of composite increased with increase in BC sheets in PO matrix. It could be further used to develop military products that require strong and lightweight feature [82]. BC fiber reinforced unsaturated polyester (UPE) composites were fabricated using the resin transfer molding method and exhibited higher fiber–resin adhesion strength [83]. BC–montmorillonite (BC–MMT) composites were prepared by impregnation of BC sheets with MMT suspension for biomedical applications. The mechanical and thermal properties of BC–MMT composites were significantly improved compared to those of the pure BC [84].The ex situ structural modifications of BC for the water-holding capacity (WHC) and WRR (water release rate) when studied by combination with MMT resulted that the WHC and WRR were dependent on the nature and arrangement of the composite materials on the surface and in the matrix of the BC sheets [85]. Freestanding BC–graphene oxide (GO) composite membranes with high mechanical strength were developed by Fang et al. [86] for selective ion permeation with high mechanical strength and structural stability membrane. The resulting BC + GO membrane demonstrates excellent permeation characteristics for separation of different inorganic/organic ions with different size from nano- to angstrom unit. Hence this composite found application in water purification, medicine, and pharmaceutical and fuel separation [86].

A hydrophilic biocompatible polymer, polyvinyl alcohol (PVA) is used in combination with BC to form biocompatible nanocomposites. It is a promising material for cardiovascular soft tissue replacement applications based on mechanical properties similar to that of cardiovascular tissues, such as aorta and heart valve leaflets [38, 39]. Preparation and in vitro characterization of BC/PVA hydrogel composite for its potential use as artificial cornea biomaterial were developed. BC/PVA hydrogel composites were synthesized by freezing–thawing method. The desirable properties as artificial cornea replacement biomaterial including high water content, high visible light transmittance, suitable UV absorbance, increased mechanical strength, and appropriate thermal properties were observed for BC/PVA hydrogel composite [87]. Hydrogels have characteristic moist wound dressing properties which was explored with a loading of silver on BC surface and confirmed for antimicrobial activity against bacterial pathogens like *S. aureus* and *P. aeruginosa*; thus it is confirmed as antimicrobial wound dressing material [88]. The potential of nanosilver impregnated BC was determined for sustained release antimicrobial wound dressing material by evaluating swelling ratio, mechanical properties, and antimicrobial activity [89].

Various cellulose–chitosan composite materials have been developed owing to the ability of ionic liquids to codissolve cellulose and chitosan. For example, Sun et al. [90] prepared cellulose–chitosan beads for heavy metal ion adsorption. Cellulose–chitosan microfibers by electrospinning were developed by Park et al. [91]. Stefanescu et al. [92] investigated the preparation and characterization of cellulose–chitosan films. Peng et al. [93] reported the preparation of magnetic cellulose–chitosan composite microspheres and their application in laccase immobilization. The lipase from *Candida rugosa* was immobilized on BC–chitosan by covalent cross-linking and physical adsorption [94]. The BC tubes have competent mechanical properties and high thermal stability to work as artificial blood vessel with intricate nanofiber architecture. With the high oxygen permeability of PDMS (polydimethylsiloxane) as a tubular template material, a series of BC tubes was biosynthesized from *Gluconacetobacter xylinum*. BC tubes also found potent to be applied as tubular scaffold materials for tissue engineering purpose [95, 96]. The modification of cellulose fiber used in the hydrogel formulation would affect its performance in hydrogel formation. The increase of surface on the nanocellulose fiber leads to more interaction and also increases the thermal stability. The micro- and nano-BC particle hydrogel with acrylic acid when compared based on properties like glass transition temperature and pore arrangement affecting the swelling degree, the nanocellulose hydrogel show improved performance. Thus it was confirmed that improved hydrogel could be formed by modifying the BC fibers [17]. One well-known method of designing composite materials with improved functional properties is the synthesis of compositions possessing the structure of interpenetrating polymer networks (IPNs) [97].This method was used for developing the hydrogel consisting of cellulose–polyacrylamide (PAAm) and cellulose–polyacrylic acid (PAA) compounds [98]. These authors suggested that anisotropy of mechanical properties of BC–PAAm hydrogels is associated with structural features of BC. Magnetic nanoparticles (Fe_3O_4) were incorporated into BC matrix by ammonia

gas-enhancing in situ coprecipitation method to produce magnetically responsive BC sheets [99]. Chondroitin is well known for the beneficial effects on joint pain, improving joint mobility and increasing and protecting the cartilage. This supplement is recommended for elderly people and athlete [101]. BC and chondroitin sulfate hydrogel was developed for dental material scaffolds and drug delivery system. Good swelling profile and active drug release rate were observed for drug delivery [102].

These and many more compounds were utilized for the composite BC hydrogel formation. The significant composite comprising BC hydrogel has been summarized in Table 1.

4 Mechanism of Formation of BC Hydrogel with Improved Characters

BC is having three-dimensional (3D) nano- and micro-fibrous porous network with remarkable and potentially tuneable properties including low density, high specific surface area, high sorption capacity, high strength, and high aspect ratio [106, 107]. The water content of BC accounts for over 98%, and its capacity for liquid sorption has been reported to be outstanding [108, 109]. Mentioned properties turned BC into an ultrafine scaffold capable of being bind with various composite materials. BC is considered to be one of the most effective reinforcement materials. Although BC hydrogel form is its natural form, the dehydrated membrane has been focused in research worldwide [103]. Hydrogel has closer fibers than the dry BC membrane. X-ray diffraction shows higher differences in crystallinity as BC mats were amorphous, while hydrogel shows much clearer peaks and better calcium phosphate phase definition [103].

In consonance with Thompson et al. [12], BC has "tunnels" oriented mainly in the vertical direction; these tunnels are formed by bacteria during biosynthesis. "Walls" of such tunnels can be condensed by congestions of the rigid chain microfibrillar BC ribbons, and these ribbons are able to mechanically reinforce hydrogels under compression in the vertical direction. For example, tunnel lacunas in the BC structure are filled with relatively soft polyacrylamide chains resulting in lower compressive stiffness in the direction along the surface of the BC [110].

The BC is highly crystalline due to its structure, but it observed to decrease crystallinity when grafting of acrylamide through cross-linking in the presence of microwave irradiation was done which ultimately results into superabsorbent hydrogels with smart-swelling properties. In the presence of microwave irradiation, the hydrogels were synthesized in a NaOH/urea aqueous system using methylene bisacrylamide as the cross-linker which has application potential for oral drug delivery. Microwave irradiation has the advantage that it improves the degree of grafting with low energy, less time, and low production cost [111, 112]. Gelatin- and BC-based hydrogel composite involved glutaraldehyde as a cross-linking agent. H-bonds were formed via the reaction between the amine and hydroxyl groups, which were the functional groups of the gelatin and BC, respectively [113].

Table 1 Summary of significant composites constituting bacterial cellulose hydrogel

Sr. no.	Composite	Application	Reference
1	Carboxymethyl cellulose	Drug loading and controlled release of drug	[63]
2	Polyvinylpyrrolidone	Soft tissue replacement, wound management	[63]
3	Gelatin	Wound dressing, drug delivery system, tissue regeneration	[13, 60, 76]
4	Chitosan	Scaffold material in tissue engineering, immobilization of proteins	[42, 94, 100]
5	Starch	Reinforcement agent for bionanocomposites	[43]
6	Alginate, sodium alginate	High strength DN hydrogel	[44, 45, 60]
7	Acrylic acid	Controlled drug delivery, burn wound healing	[46, 47, 68]
8	Graphene oxide	Water purification, food industry, biomedicine, and pharmaceutical and fuel separation	[86]
9	Montmorillonite (MMT)	Biomedical application dressing material	[84, 85]
10	Polyester (PO)	Reinforced scaffold; strong and lightweight military products	[82, 83]
11	Vaccarin	Cell growth carrier, wound dressing	[81]
12	Hyaluronic acid	Wound healing, tissue engineering	[28, 77, 78]
13	Chondroitin sulfate	Space controlled drug delivery, dental material scaffold	[101, 102]
14	Ca phosphate	Drug loading scaffold, bone substitute	[103]
15	PHEMA (2-hydroxyethyl methacrylate)	Contact lenses and optic components for biosensor	[51]
16	Polyacrylamide	Tissue engineering cartilage replacement	[98, 110]
17	Polyaniline	Electrically conducting bioanode, electrode material for supercapacitors	[53, 54, 56]
18	Gellan gum	High strength DN hydrogel synthetic connective tissue	[60]
19	L-Carrageenan	High strength DN hydrogel synthetic connective tissue	
20	Hydroxyapatite	Bone scaffold platform, biomedical membrane	[69, 70]
21	Acrylamide	Drug delivery	[67]
22	Polyvinyl alcohol	Cardiovascular soft tissue replacement, artificial cornea biomaterial	[38, 39, 87]
23	Conducting polymer	Implantable device	[71]
24	Polylactide and glycidyl methacrylate	Skin repair material	[74]

(*continued*)

Table 1 (continued)

Sr. no.	Composite	Application	Reference
25	Polypyrrole	Microbial fuel cell (MFC)	[57]
26	Guar gum	Bioactive wound dressings, scaffolds for cellular growth, sustained drug release	[79]
27	Collagen	Wound dressing for skin regeneration	[80]
28	Silver	Antimicrobial wound dressing	[88, 89]
29	Cadmium	Photocatalytic activity	[105]
30	Titanium oxide	Photocatalytic activity	[104]

The physical or chemical stabilization of aqueous solutions of cellulosic leads to the formation of cellulose hydrogels. The composite hydrogel could be synthesized by addition of either natural or synthetic polymer/other compounds to improve the specific properties [114, 115]. The gelation mechanism involves hydrophobic associations among the macromolecules possessing the methoxy group. The polymer chains in solution are hydrated and merely intertwined with one another at low temperatures. The macromolecules gradually lose their water of hydration with increase in temperature up to the polymer–polymer hydrophobic associations that have effect forming the hydrogel network.

Depending on the cellulose composite to form and components used, a number of cross-linking agents and catalysts can be employed to form hydrogels. The most commonly used cross-linking agents for cellulose include epichlorohydrin, urea derivatives, aldehyde-based reagents, aldehydes, carbodiimides, and multifunctional carboxylic acids. The radiation-induced cross-linking has got the recognition as no need for any additional chemical reagents, controlled process, and simultaneously the sterilization of the product can be carried out for biomedical applications. The high-energy radiation associated with discontinuation of polymeric chain of the cellulose [116]. BC reacts with different composite materials by different mechanisms like doping (with silver nanoparticles) [88], chemical oxidation (by polyaniline) [53, 54], hydrogen bonding (with polyacrylamide) [98, 104], blending (with carbon nanotubes) [117], cross-linking (with gelatin by glutaraldehyde as cross-linker), etc. [60, 76]. Some representative examples have been shown in Fig. 2.

5 Exploration of BC Hydrogels in Different Domains

BC hydrogels have applications in diverse fields like biomedicine, agriculture, environment, etc. Fig. 3.

5.1 Biomedical Applications

Cellulose-based superabsorbent hydrogels are widely used in the biomedical field, for instance, drug delivery, tissue engineering, cell bioreactors, and micropatterning neural cell cultures [16]. Patterned macroporous BC (PM-BC) scaffold was developed

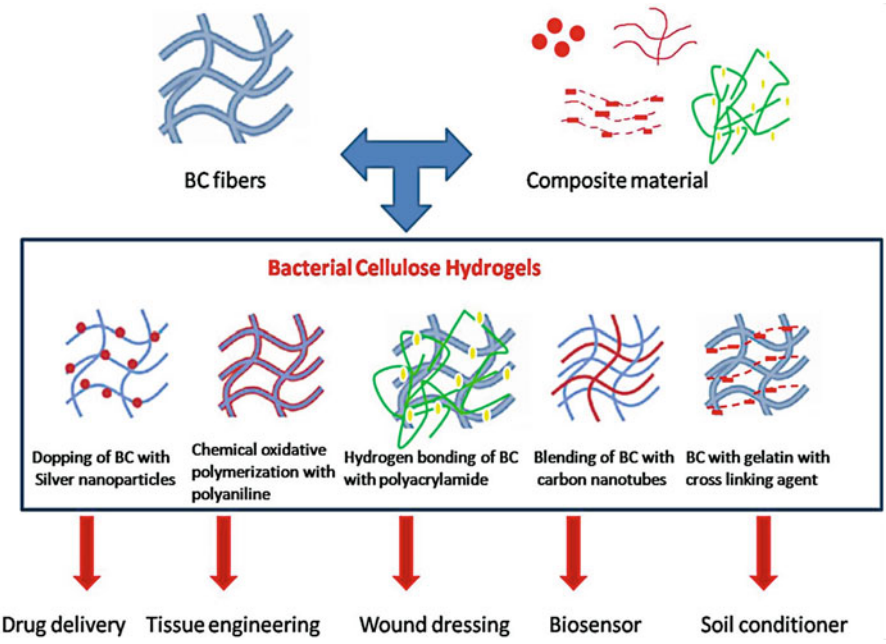

Fig. 2 Synthesis of composite bacterial cellulose hydrogel with representative examples

using the infrared laser micromachining technique. The PM-BC scaffolds were found to be able to promote cellular adhesion and proliferation on the scaffolds and allow for cell infiltration into the PM-BC scaffolds. The BC scaffolds with laser-patterned macropores were promising for the in vitro 3D culture of breast cancer cells [118]. BC promotes the wound healing by keeping the wound moist by controlling the wound exudates [34]. The commercially available BC wound dressings in the market are Biofill®, Bioprocess®, and XCell® [119]. Various studies indicate that local applications of BC membranes improve the healing process of burns and chronic wounds [48]. A recent study used the never-dried BC membranes in order to treat patients with severe second-degree burns. Hydrogel adsorbed on the wound surface maintains the moisture sufficiently in the wound area. Consequently, it was recommended as an ideal wound dressing material. BC–hyaluronic acid hydrogel encourages a good proliferation of keratinocytes, as proved in in vitro culture [28].

The double network BC–conducting polymer hydrogels are biphasic Janus hydrogels which integrate electroactivity with biocompatibility and might provide a biology–device interface to produce implantable devices for personalized and regenerative medicine [71]. Bacterial nanocellulose (BNC) is very attractive to use as a scaffold to use in tissue engineering. The addition of porous wax particles in the fermentation broth leads to macroporous BNC with excellent interconnectivity. BC has interesting features of nanostructure and morphology very similar to collagen which makes BC an attractive choice to support and immobilize the cell. The architecture of BC materials can be engineered over length scales ranging from

Fig. 3 Application areas of bacterial cellulose hydrogels

nano to macro by controlling the biofabrication process. BC fibers are very strong and, when used in combination with other biocompatible materials, produce nanocomposites particularly suitable for use in human and veterinary medicine [120].

The drug loading and release with BC is another fascinating exercise creating attention. The BC gradually released up to 90% of the drug within 24 h as well as the antibacterial activity of drug-loaded BC established which prove the nontoxic biocompatible nature for drug loading and release potential of BC [121]. Graphene oxide–BC nanocomposite is a new drug nanocarrier as a potential choice for drug delivery system [122].The antibiotic drug tetracycline hydrochloride (TCH)-loaded BC composite membranes were also evaluated for the drug release, antibacterial activity, and biocompatibility [123].

5.2 Agriculture Applications

In a dry and semiarid environment, water retention capacity or moisture retention plays a key role in the growth and establishment of crops. Soil conditioners are competent enough to increase water-holding capacity by reducing infiltration rate and improving water conservation of soil [124]. One of the highly effective methods to enhance structure is by adding synthetic and natural polymers that improve soil

cohesion, porosity, maximum water-holding capacity (MWHC), and various beneficial soil properties. The synthetic soil conditioners like polyacrylamide, glycols, and hydrogel have major drawbacks like cost, carcinogenicity, sources of origin, etc. Natural polymers are degraded usually by relatively benign route. Cost-effective, biodegradable, and eco-friendly nature of biopolymers makes it an important alternative to synthetic polymers. The improvement in soil physical properties like porosity accompanied by an increase in water-holding capacity was reported by use of BC hydrogel [125]. The amendment in porosity with higher water-holding capacity proves BC as natural soil conditioner [16].

5.3 Environmental Applications

Different hydrogels with diverse functional groups have the ability to complex with dyes [126]. Particularly BC which is excellent biocompatible biomaterial and has a less latent toxic effect compared with a synthetic polymer bind with azo dyes, for example, BC grafted with acrylic acid has successfully explored for removal of methylene blue from aqueous solution [127]. Cd and TiO_2 supported on BC nanofiber used as photocatalysts for degradation of a model pollutant, methyl orange [104, 105]. BC has also been reported for bioadsorption of heavy metals like Pb, Cd, and Ni [125].

The BC–chitosan hydrogel beads were employed as enzyme supports for lipase immobilization by physical adsorption and covalent cross-linking and further could be used to immobilize proteins for various environmental applications [94, 128]. Wang et al. [129] developed a high performance biosensor based on gold nanoparticle–nanocellulose hybrid composites for immobilization of heme proteins such as horseradish peroxidase, hemoglobin, and myoglobin which are used as sensors for the diagnosis of metabolic diseases like skin lesions, edema, liver damage, and pancreatitis. In potential water remediation system, the reduction of nitrates for water denitrification was reported with Cu–Pd nanoparticles on BC nanofibers [104].

6 Conclusion

Several groups are involved in the investigation of macroporous BNC scaffold for regeneration of the bone, cartilage, urethra, and bladder. Different approaches are used to create different pore size, different cultivation condition and time, and posttreatment like freeze-drying for getting the essential desirable structure. Further insight is required with respect to pore size in a never-dried state in different types of BC like self-assembled, oriented BC and multiform BC. Composite preparation using BC in conjunction with other polymers needs to be explored, and the research on BC for application in skin tissue engineering is required to be addressed. The BC potential as a drug carrier and for a controlled premature release of drug is a remarkable appliance. The comprehensive studies are needed to determine the role of surface functionalities of materials which makes the hydrogels and impart the

characteristic properties for drug delivery. On this background, there is need of current scientific knowledge of technological advancement in biological methods for the invention of next-generation biomaterial-based hydrogels. In summing up, for BC-based hydrogel like lucid intend material, unique chemistry study with noteworthy in vitro, in vivo, and ex vivo evaluation with diverse composites would be a matter to focus in the projected future. BC is a versatile biomaterial for application in various domains. The prospect for the various biomedical applications of BC hydrogel-based materials is obligatory needed a research to make BC as expected to be a commodity material in various fields.

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Importance of Multi-Stakeholder Initiatives in Applications of Bacterial Cellulose-Based Hydrogels for Sustainable Development

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Contents

Abstract

Currently, there is a wide range of consensus and awareness regarding whether nature can help or provide feasible solutions to achieve more inclusive and sustainable growth in a smart, "engineered" way. Similarly, for sustainable development the appearance of multi-stakeholder initiatives (MSIs) among

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companies, governments, and civil society organizations is also remarkable as they enable them to motivate and share knowledge, expertise, technology, and financial resources. This crucial idea arises in relation to how nature-based solutions provide sustainable, cost-effective, multi-purpose, and flexible alternatives for various objectives. For example, applications of bacterial cellulose (BC), which is synthesized by various bacteria, have great potential in a number of fields, such as food, biomedical material, cosmetics, healthcare, paper making, and other applications, but has a mostly untapped potential for contributing to cellulose-based hydrogels – that is, its smart applications. This work adds detailed discussion of aspects of MSIs (science, policy, business, and society, including small and medium-sized enterprises [SMEs] and public and private investors) relating to BC and BC-based hydrogels (BHs) and the various novel applications that promote the innovative, multi-purpose, dynamic capability intended for commercially exploitable BC and BC-based biocomposite products, in the form of hydrogen. To exploit new and emerging research opportunities for BC and BHs, this work reveals the significance of building an innovative platform such as the European Knowledge-Based Bio-Economy (KBBE) to bring together all of these advancements in cellulose-based hydrogels in simulated pathways for novel applications.

Keywords
Bacterial cellulose · Hydrogels · Multi-stakeholders initiatives (MSIs) · Societal challenges · Sustainable

1 Introduction

To address the sustainable development of bacterial cellulose (BC)-based hydrogels (BHs), nature-based solutions (NBS) offer viable options for meeting the societal challenges that are inspired and supported by nature. These NBS provide sustainable, cost-effective, multi-purpose, and flexible alternatives to achieve several objectives. For example, BC, which is synthesized by various bacteria, has unlimited potential in its application in many fields including the food industry, healthcare applications, paper making, and several other but generally unexploited uses for contributing to cellulose-based hydrogels – smart applications. In response to these challenges, this chapter provides a holistic framework that systematically identifies how a multi-stakeholder platform (MSP) could provide both synergies across NBS, but also co-benefits in other different elements (socio-cultural, socio-economic system, environment, biodiversity, ecosystems, and climate), particularly in urban areas [1].

According to the European Commission [2], NBS can be defined as "solutions that are inspired and supported by nature, which are cost-effective, simultaneously provide environmental, social and economic benefits and help to build resilience".

This chapter discusses and anticipates the importance of multi-stakeholder initiatives (MSIs; science, policy, business, society, including small and medium-sized enterprises [SMEs], public and private investors) on BC and BH for numerous applications and in encouraging the innovative, multi-purpose, and dynamic capabilities intended for commercially exploitable BC and BC-based biocomposite products in the form of hydrogels. As a final point, it is expected that MSIs could build a multi-level (local, regional, national, and European Union [EU]) innovation platform to meet the societal challenges of Horizon 2020. In continuing with this discussion, it is necessary to mention that MSIs are vital in today's world to meet sustainable development goals (SDGs). Based on the World Bank's conference report entitled "Increasing the Effectiveness of multi-Stakeholder Initiatives Through Active Collaboration", these types of initiatives can be considered the best hope of identifying and supporting long-term solutions (especially for large and complex problems) [3, 4].

In addition, this chapter highlights the significance of building an innovative platform such as the European Knowledge-Based Bio-Economy (KBBE) to exploit new and emerging research opportunities on BC and BH that address social, environmental, and economic challenges and committed innovation partnerships in order to bring together all of the advancements of cellulose-based hydrogels in simulated pathways and for novel applications. The chapter further describes and determines the sustainable development path and how different firms, people, and knowledge at a national and international level are making civil society organizations (CSOs), non-governmental organizations (NGOs), individuals, and institutions more innovative and competitive in order to create new jobs and economic growth through the manufacture and delivery of new nature-based innovative products and services.

2 The Multi-Stakeholder Initiative (MSI) Perspective and Nature-Based Solutions

Current societal challenges, that is, socio-economic and socio-political problems as well as developments, are many, multifaceted, and crucial, and range from societal and environmental change to energy efficiency and security. Regarding this problem, there is significant congruence between the gap in social and economic growth and the well-being of society, which is rapidly growing. Correspondingly, during the twenty-first century, research and innovation has also become one of the foremost stimuli of social-economic growth nationally and internationally. In response to this vital situation of societal challenges, this section discusses the prospective awareness and emergence of MSIs that enhance the role and effectiveness of MSIs and partnerships as a model and critical force in economic social development and strategic planning. This is a subject which fascinates the attention of numerous policy makers, academics, technocrats, clinicians, and researchers from developing and developed

countries with regards to scaling up the innovation on biomaterial products such as BC and BH, their resources, and action in order to deliver the SDGs.

This section also attempts to highlight the importance of multi-stakeholder partnerships which deliver a wide and numerous ranges of institutional arrangements for expanding collaboration between government, business (both private and public sector actors), civil society, and other multi-lateral agencies to address economic development challenges that generate commercial value in society. In this change-over period, the impression of MSIs has emerged as a significant building block in new governance arrangements responding to the press, often global sustainability challenges, and meeting societal challenges [5].

Several researchers such as Matten and Crane [6] have expressed their opinion on MSIs as a form of collective self-regulation when governments are either unwilling to or incapable of providing adequate regulation at the national or global level. In relation to this discussion on how MSIs can enhance the sustainability of BC and BH, it is essential to mention that the MSIs approach in management science is a local, regional, national, and international development strategy that seeks to escalate the efficiency and efficiency and effectiveness, i.e. well-being economic systems. It is a strategic approach of SDGs targeted towards the upcoming new program of Horizon 2020 in order to support responsible research and innovation (RRI), especially in innovative biomaterials production and its application for promoting innovative, multi-purpose, effective capability and commercially exploitable BC and BC-based biocomposites (BH).

Figure 1a shows the main principle of the multi-stakeholder concept through the MSIs model and Fig. 1b illustrates the aims of the MSI support development system, which are to:

- Tackle complex sustainability problems globally;
- To create value chains within the international business environment;
- Collaborate between civil society, the private sector, and the public sector to reinforce development; and
- Overcome the major gaps in global governance.

The main concept of MSIs is composed of three main elements that achieve the following:

- Responds to the limited capacity and resources of individual societal sectors, such as:
  Government, business, and civil society;
- Combines the capacities and resources of several stakeholder groups; and
- Solves the complex sustainability problems on their own.

From the functional and features perspective point of view, it can be said that MSIs act as a service provider of an effective application-oriented toolbox for

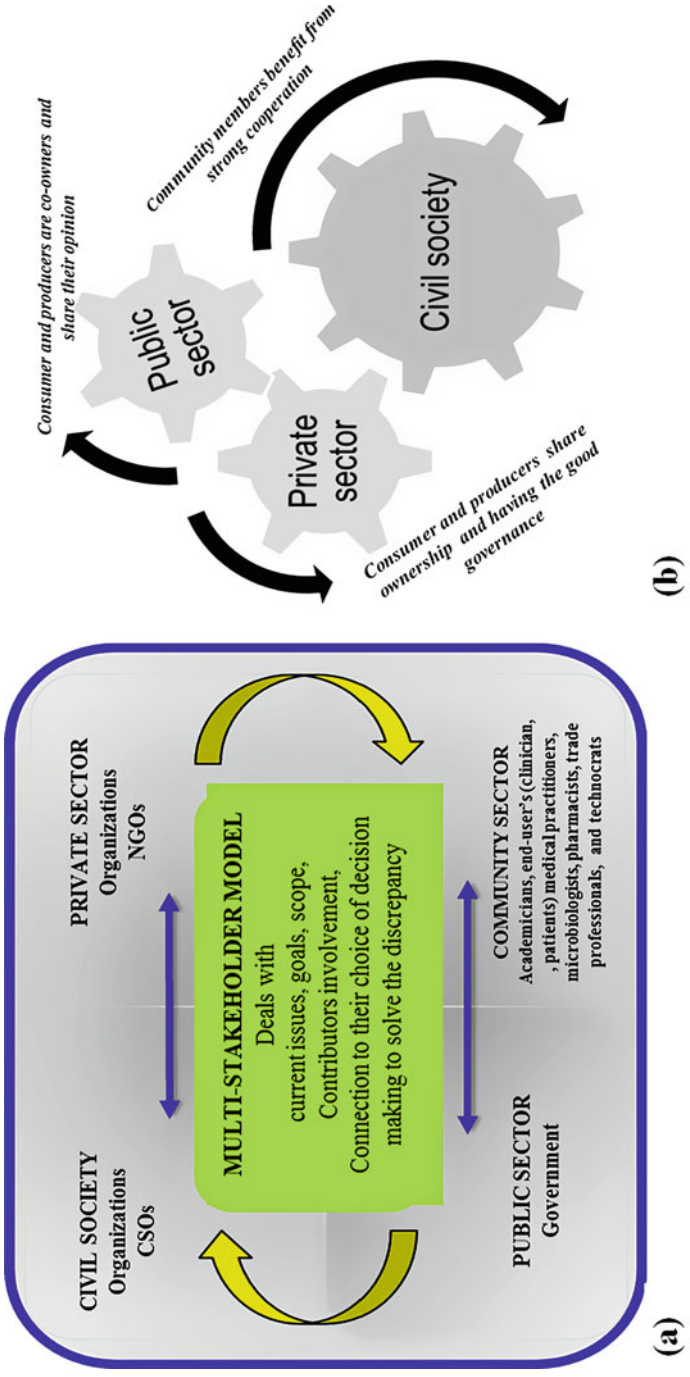

Fig. 1 (**a**) Multi-stakeholder initiatives (MSIs) model. (**b**) MSIs support development system

support as well as combining many stakeholders in a particular industry sector, whether it be a single issue or at a regional level. In this regard, it is necessary to mention that MSIs are mainly considered by Standards schemes, certification systems, joint stakeholder initiatives, roundtable dialogues, common codes of conduct, and joint funding for research and innovation. Moreover, while addressing the impact of MSIs for sustainable development of the various applications of BHs, it is important to discuss Welford's [7] proposition regarding how MSIs can inspire the BC-based products' fabrication, distribution, and consumption processes to be more sustainable and ethical through three key elements, by:

(i) Involving a broad range of legitimate stakeholders, including businesses, NGOs, local communities, and governments;
(ii) Establishing a sound multi-stakeholder governance structure that will ensure different voices, opinions, and possible solutions for BC and BC-based products (in the form of hydrogel); and
(iii) Designing stakeholder engagement mechanisms that enable the views and concerns of a broad range of impacted stakeholders, i.e. science, policy, business, society, including SMEs, public and private investors (medical practitioners, patients, and technical community), to be gathered, with an emphasis on those who might be exposed and ensuring full participation [8].

The presence of social entrepreneurs as new actors on the innovation scene is essential in assessing the societal dimensions. Accordingly, the Organisation for Economic Co-operation and Development (OECD) [9] and its innovation strategy [10] set out five priorities for policy makers, businesses, and civic societies to improve innovation performance and achieve greater responsibility and growth of nature-based solutions, such as BC and BH. These priorities are to strengthen investment in innovation and foster business dynamism that enables them to shape an efficient system of knowledge creation and diffusion, seize the benefits of the digital economy, foster talent and skills and optimize their use, and improve the governance and implementation of policies for innovation [8]. Moreover, the MSIs concept has emerged as a phenomenon with high practical relevance in relation to sustainable development. At the same time, These priorities are equally stimulating from a theoretical perspective because of their integral environment. According to Prakash and Gugerty [11], MSI approaches offer voluntary regulation as a means to overcome the current global governance gaps; for example, no organization/institutions are obliged to join the MSIs and adhere to their standards. Similarly, Konefal [12] also stated that the idea of MSIs enables any discrepancy and interruption to be avoided as well as allowing sustainability metrics to be directed towards ones that are congruent with the existing business administration and marginalize metrics that have the potential to disrupt regime processes. The latest generations of biomaterials are now becoming more and more sophisticated, and as a result combination products and smart materials may face the limitations of standard in vitro and in vivo evaluation techniques. Therefore, regulatory agencies continuously raise questions about the information required for any new devices: their purity and

characterization, safety and performance evaluation, and mechanism of action. In these respects, partnerships in the form of MSIs (between academics, clinicians, policy makers, technocrats, and researchers from developing and developed countries) may increasingly be required during the course of commercial development of new biomedical products such as BH concepts and technologies [13].

On the other hand, the appearance of the concept of NBS in environmental and natural sciences was initiated by several international organizations, such as the International Union for Conservation of Nature (IUCN), EU and the World Bank, in order to cope with environmental extremes. The purpose of this emerging approach is to provide novel solutions that have benefits for societal development and address a variety of environmental, social, and economic challenges in sustainable ways [14, 15]. More precisely, NBS can be defined as actions to protect, sustainably manage, and restore natural or modified ecosystems that address societal challenges effectively and adaptively, simultaneously providing benefits for human well-being and biodiversity. However, NBS is a relatively "young" concept, and is still in the process of moving towards an operational framework that can guide applications of the NBS concept [14].

The use of NBS to reframe the strategy- and policy-related debates around urban sustainable development has been rapidly increasing recently. However, there has been very limited research on implementation of NBS, or on understanding in what way NBS may come to be properly contested. In this context, this section designates innovative biomaterials smart applications as NBS[1] to meet the societal challenges and provide solutions for sustainable development of BC and BH and their applications that are inspired and reinforced by nature, which will be inexpensive and simultaneously offer environmental, social, and economic benefits in order to support and form communal resilience.

2.1 Nature-Based Solutions and Sustainable Development

The quest for sustainable development has become one of the most significant programs of EU research and innovation policy for NBS such as BC-based BH for various applications. According to the report by Brundtland, the modern concept of sustainable development was first defined by Brundtland and published by the United Nations World Commission on Environment and Development in 1987 [16, 17] in order to find possible solutions for both environment protection and economic growth. In this context, the bacteriological researchers mainly undertook NBS initiatives relating to schemes to enable and facilitate them to establish competent sustainable biosystems for the production of industrially beneficial substances and materials from renewable agro-biological resources [18].

In this regard, the mission of innovative biomaterials products such as BH as NBS is to uniquely contribute to the dialogue between and partnering of stakeholders from various sectors focusing on BC production of agro-biological resources such as

[1] https://ec.europa.eu/research/environment/index.cfm?pg=nbs

apples, dragon fruit, pineapples, watermelon, sugarcane, and so on. NBS are considered to be actions that empower to protect, sustainably manage, and restore natural or modified ecosystems in order to address societal challenges effectively and adaptively, simultaneously providing human well-being and biodiversity benefits [19]. Thus, it essential that these BC and BC-based products, for example hydrogel (BH), establish sustainable production and consumption. On the other hand, BC has huge potential to reshape our daily lives and industry: the contribution of BC to the environment through its biodegradability is quite obvious (e.g., by using cellulose abstracted from apple juice) [20–22], which will put more emphasis on new economic opportunities through various applications such as biomedical, food, and agricultural and industrial applications of BC and BC-based products as NBS.

2.2 Sustainable Development of Bacterial Cellulose (BC)

Cellulose is the Earth's major biopolymer and is of tremendous economic importance globally. Cellulose is the main constituent of cotton (over 94%) and wood (over 50%) – together, cotton and wood are the foremost resources for all cellulose products. Traditionally, cellulose is taken from plant resources, but to achieve pure cellulose requires energy and chemicals, which is often harmful to the environment since unwanted lignin must be removed and then the cellulose must be bleached [23]. Although cellulose is a well-known plant product, some bacteria have gained attention as an alternative and sustainable source of cellulose, with *Komagataeibacter xylinus* (the most extensively studied species is *Gluconacetobacter xylinus*, formerly known as *Acetobacter xylinum* and now reclassified as *Komagataeibacter xylinus*) being a representative BC producer. BC is a nanomaterial produced by various strains of *Acetobacter* species and also strains of *Pseudomonas*, *Achrobacter*, *Alcaligene*, *Aerobacter*, and *Azotobacter* [24]. *Acetobacter xylinum* is one of the species capable of large-scale production of cellulose in culture medium-containing carbon and nitrogen sources in either a static or agitated environment [25]. BC and plant cellulose have the same molecular formula, but the former has some supplementary competitive advantages that have attracted the attention of material scientists, biotechnologists, and biomaterialists in the quest to produce innovative BC and BC-based biocomposites. It should be mentioned that BC has some excellent physical properties in comparison with plant cellulose that enhance its mechanical stability, tensile strength, thermos ability, crystallinity (i.e., ultrafine fibrous structure), purity, and biocompatibility (i.e., biologically non-toxic and no immune responses) [26, 27].

Therefore, to enhance the sustainability of BC and also the process of achieving commercial-scale production of BC apparently depends on raising public awareness of all aspects of cellulose, extending from its fundamental biosynthesis and structural properties to its biotechnology applications. Consequently, education and communication among professionals are necessary. International collaboration between scientists from many fields, including botany, microbiology, chemical engineering, forestry, mechanical engineering, polymer science, textiles, food products, marketing,

economics, and business, is required to fully realize the merits of a new resource for a widely used product. Though the commercialization process has not been remarkable, the excellent biocompatibility of BC has motivated development of BC-based biomedical products such as bone tissue scaffolds, artificial blood vessels, artificial skin, and dental implants. High-purity BC obtained through fermentation also facilitates separation and purification and further physical/chemical modifications [28, 29]. This could be an excellent opportunity to take advantage of for new product development. With such competitive advantages, the possible applications of BC have been expanded from the food industry to cosmetics, biomedical, and even electronics industries. Some well-known commercialized BC-based products are those produced by Nata Company (Philippines) [30]. Researchers across the world have used different methods to produce products using BC and microbial cellulose producers have now shown that there is increased demand for BC-based products such as wound dressing materials and facial masks [31, 32]. It is paradoxical that the demand now outpaces the supply of BC (i.e., microbial cellulose), largely due to lack of investment in innovative product research and development (R&D) regarding fermentation processes to optimize microbial cellulose production on a large scale.

2.3 BC and BC-Based Hydrogel (BH) Production

The application of BC synthesized by many bacteria has great potential in various fields such as food, biomedical material, paper making, and transducer diaphragms. BC is one of the key biopolymers/biomaterials. In general, the substrates for BC production are low-cost and nature based, such as cotton-based waste textiles, wheat straw, elephant grass acid hydrolysate, or other residues from agro-forest industries. However, when applied in the food or healthcare industries, more suitable substrates to use for BC production come from food resources, such as corn steep liquor, molasses, konjac powder hydrolysate, and so on. Common fruit juices, such as from oranges, apples, pineapples, grapes, lychee, and so on, have proved to be promising substrates for BC production. BC, as a natural biopolymer produced by non-photosynthetic bacteria, can contribute to green growth, climate action, and promote innovation with nature. Presently, organic polymers are being explored extensively for the fabrication of hydrogels, due to their biodegradability, biocompatibility, non-toxicity, and availability. Consequently, considerable attention has been paid to BC, a natural polymer, because of its high mechanical strength, thermal stability, biocompatibility, and purity [33]. However, its application in the synthesis of hydrogels is limited by its insolubility in common solvents due to strong inter- and intramolecular hydrogen bonding.

Thus, stabilization of BC in appropriate solvents could extend its application in the fabrication of film, hydrogels, and membranes, and improve its purity and mechanical strength for pharmaceutical and biomedical applications. Hydrogels are physically or chemically cross-linked three-dimensional (3D) hydrophilic polymeric networks capable of absorbing large amounts of water (or biological fluids) and swelling [34]. Any (semi-)flexible polymer is able to virtually formulate

hydrogels in a variety of physical forms including slabs, membranes, beads, microgels (microspheres), and nanogels (nanoparticles), and once freeze-dried or supercritically dried, hydrogels become cryogels or aerogels, respectively. Hydrogels are joined together by either physical interaction (chain entanglements, van der Waals forces, hydrogen bonds, crystallite associations, and/or ionic interactions) or chemical cross-links (covalent bonding). Research shows that BH have been prepared and blended with carboxymethyl cellulose (CMC) and polyvinyl pyrrolidone (PVP) by using moist heat treatment. In addition to the properties of BC–CMC and BC–PVP, these hydrogels were compared with pure BC, CMC, and PVP hydrogels by measuring their structure and morphological and viscoelastic properties. Through the morphological images, alignment of the porous flake-like structures allows us to understand clearly the inter-polymeric network of the BH [35].

It can be said that hydrogels formed from self-assembled biopolymer networks are particularly noteworthy in that they better mimic the microenvironment of native tissues as they show structural, chemical, and mechanical similarities to the extracellular matrix and good biological compatibility. Tissue engineering scaffolds play a fundamental role in providing an intuitive environment that mimics tissue cells, with the aim of promoting regeneration of the desired tissue [36]. One of the main applications of hydrogels is the treatment of wounds, an application that usually demands the use of biomaterials that promote tissue repair or regeneration and prevent infections. A schematic diagram of BC production is depicted in Fig. 2. It shows the plan and steps involved in BC production from different kinds of apple juice (as a lab-scale experiment).

Fresh apple juice (AJ) was prepared and sterilized, after which the AJ is used for BC production. Apples (golden delicious [GD], jonagold [JO], and gala [GA]), the main raw material, were purchased from local supermarkets in Zlín, Czech Republic. The production of BC was undertaken using three different kinds of apple juice (AJ_GA, AJ_JO, and AJ_GD). Initially, the pH of all three types of AJ (AJ_GA, AJ_JO, and AJ_GD) remained unaltered, and fermentation conditions were maintained at 30 °C for 15 days [20, 22], achieving a good quantity of BC as the yield substance.

2.4 Novel Applications of BC and BH

In order to become familiar with the novel applications of BC and BH, it is important to understand the cross-linking factors of hydrogels that make it easier to consider it as a novel biomaterial product. Basically, hydrogels or water-containing gels are cross-linked polymeric materials that sustain a distinct 3D structure and are characterized by both hydrophilicity and insolubility in water. They can be classified on the basis of their sources (natural or synthetic gels); the nature of the cross-linking (covalent or physical gels); the nature of the network (homopolymer networks, copolymer networks, interpenetrating networks, or double networks); the presence of pores (homogeneous [optically transparent] hydrogels, microporous and macroporous hydrogels); the basis of mechanical spectra (strong and weak hydrogels); the

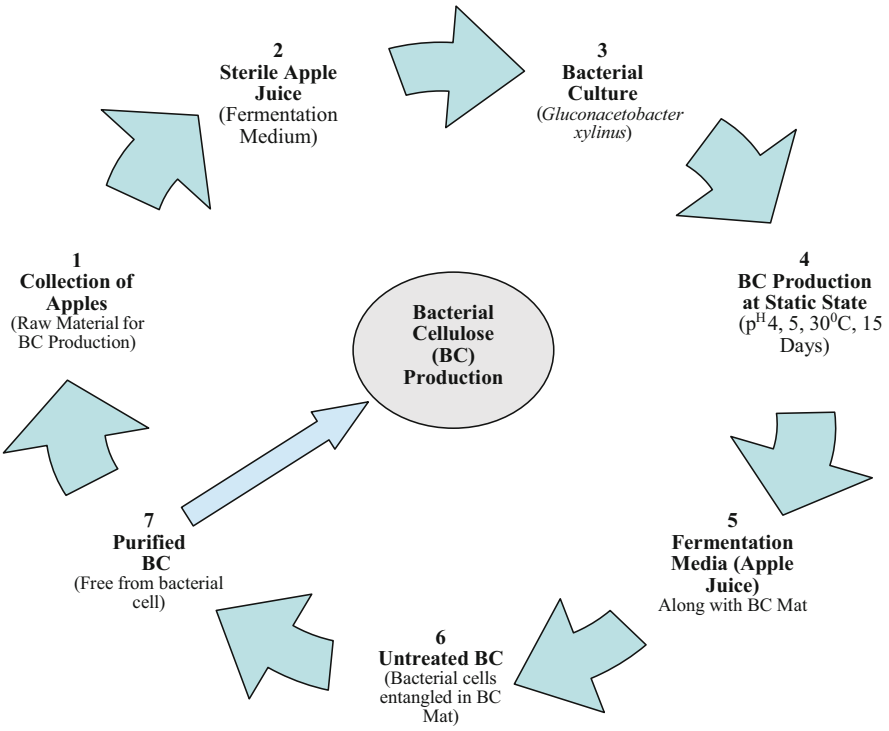

Fig. 2 Bacterial cellulose production from apple juice [20–22]. BC (Bacterial Cellulose); p^H 4, 5, temperature 30 °C

mechanism of gel formation (pseudo/unstable hydrogels, true/permanent hydrogels); and their fate in an organism (degradable and non-degradable hydrogels) [37, 38].

In 1960 Kopeček and Yang reported that hydrogels were the first innovative biomaterials rationally designed for human use. However, these hydrogel biomaterials now have a wide range of biomedical applications such as in drug delivery, contact lenses, control implants, substitutes for skin, tendons, ligaments, and cartilage, and in bone tissue engineering [39]. Hydrogels can satisfactorily be used as a dressing material in medical treatment for burns and wounds. The significance and potential application of native BC was first reported by Adrian J. Brown in 1886, and *Acetobactor xylinum*, now known as *Gluconacetobacter xylinus*, is considered to be nature's most prolific cellulose-producing bacterium. A typical single cell can convert up to 108 glucose molecules per hour into cellulose chain. Due to the development of such spun-like distinguishing features of the BC membrane, different shaped objects can be produced directly during the fermentation process, thus enabling a novel array of non-woven products. Because of such novel features of BC, a variety of product applications is possible. In view of escalating the scope of BC application (Fig. 3) in different fields, including the medical field (as wound care dressing pads, drug delivery agents [either oral or dermal], artificial skin substrates,

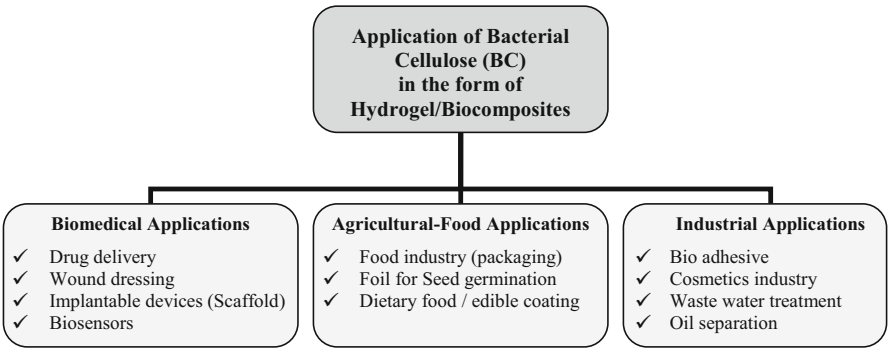

Fig. 3 Novel applications of bacterial cellulose (BC) and BC-based hydrogels in different fields

artificial bio-composite bone, etc.), effort needs to be put into fabrication of innovative BC pellets and membranes/modified BC under affordable conditions using agro-bio wastes. Also, BC-based polymer composites needed to be prepared.

Furthermore, the innovative potential of BC shows great potential, especially in medicine and pharmacy; however, the higher manufacturing costs resulting from expensive culture media limit its large-scale industrial applications. To enhance the compatibility, however, there are two different ways to reduce BC production costs: one is to genetically improve the microorganism in order to increase the productivity of BC; and the other is to replace costly culture media components with inexpensive agro-industrial waste and by-products such as sources of carbon nitrogen and microelements. During BC production, production of the mutant strain is approximately two times higher than that of the wild-type strain [40, 41].

According to a recent report, cellulose is secreted from bacterium in the form of a ribbon at a rate of 2 μm/min and is composed of approximately 46 microfibrils [42]. The second strategy is to develop culture media based on cheaper and easily available feed stocks [43, 44]. Hence, it can be emphasized that potential applications of BC increase in these areas, such as in specialty textiles, advanced functional materials, and packaging as well as biomedicine and biomedical applications [44, 45], the prime goal of MSIs being to determine the strategy that contributes to the valorization of the residues themselves and then to the global implementation of the bio-economy model.

2.5 BC-Based on Hydrogels: Prospective Application for Scientific, Technological, and Socio-Economic Advantages

2.5.1 Scientific Advantages

BC and BH advanced functional biomaterials can be developed in the field of biomedical industries through interaction and cooperation between various research disciplines such as bioscience, polymer science, materials science, analytical chemistry, nanotechnology medical science, and so on. Awareness of these new

biomaterial(s)/prototype bioreactor(s)/medical device(s) will not only be made available to established academician/researchers, but will also attract the participation of young scientists.

2.5.2 Technological Advantages

To address the technological advantages, it is necessary to mention that the initiatives of different stakeholders (science, policy, business, society, including SMEs, and public and private investors, such as medical practitioners, patients, and technical community members) will create a greater variety of potential markets for BC and BH, including product improvement and development because BC from different sources displays a large variety of structural combinations, which gives them unique properties. The scope of these products may gain commercial acceptance for different biomedical applications to catch the recent and future markets (such as BC for wound healing, skin care treatment, regenerative medicine, tissue engineering, etc.).

2.5.3 Socio-Economic Advantages

The socio-economic advantages of BC can be promoted in all kinds of biomedical as well as other applications (e.g., agricultural, food, and environmental industries). However, in most practical applications, BC may not be of impeccable quality and its cost may not be suitable for industrialization either. For economical mass production, it is essential that a culture ventilation and distress process be designed, that is, biosynthesis of BC and its application as a skin tissue repair material. The skin tissue materials derived from BC may create an enlightening perspective in the future. Similarly, BH for wound healing materials may also show superior performance in the healthcare, food, cosmetics, and other industrial fields, and will continue to be more important in the near future as well as providing an additional eco-friendly benefit. Thus, it can be expected that contemporary applications of BC such as hydrogels, scaffolds for tissue engineering, implants, wound dressing, super capacitor (e.g., BC-derived electrode and BC-based gel electrolyte) [40], optoelectronics applications, packaging, special textiles, and so on will tackle societal challenges.

3 Multi-Stakeholders' Policy Dialogue and Initiatives

In the context of the discussion around the proliferation of MSIs, this section mainly concentrates on how the understanding of the MSP will influence the novel application of biomaterials such as BC and BHs. The method of multi-stakeholder involvement will enable application of novel biomaterials in order to achieve distinct advantages of effective development of CSOs and facilitate the environment to improve and implement SDGs. It is crucial to highlight that MSIs bring together diverse actors from the public, private, and civil society sectors in order to solve persistent governance challenges such as enhancing transparency and improving responsibility for better and more sustainable development outcomes [4]. Several

researchers and economists who were interested in independent non-profit research and network working systems related to social, ecological, and economic matters for achieving sustainable development have emphasized the aim of multi-stakeholder processes to encourage and promote better decision-making through ensuring the perspectives of the main actors concerned about a particular decision are incorporated at all stages through consensus-building dialogue. This MSI approach will start with a dialogue and/or negotiation concerning smart and sustainable welfare of the society in order to meet the societal challenges through production of BC from agro-biological resources, such as apples, dragon fruit, pineapples, or watermelon. After analysis, the BC production and MSI platform development opportunities for civil society, the private sector, and the public sector, including the prospect of local, regional, national, and international development strategies that seek to escalate the efficiency and effectiveness of communities' economic systems could be recognized as the most suitable subject to concentrate on to meet these societal challenges. The smart flowchart of multi-stakeholders' individual roles in BC production from agro-biological resources in Fig. 4 demonstrates the process of sharing knowledge and good practices that will involve representatives from the spheres of business, civil society, and possibly other stakeholder groups to address the sustainability problem. The dialogue and negotiations will be associated with open communication. After successfully finding common ground, this novel biomaterials application will be able to evolve to the next phase of forming an organization, followed by implementation arrangements and continuous improvement. This will again require negotiation and/or dialogue.

3.1 Impact of Multi-Stakeholder Initiatives (MSIs) on the Changing Innovation Paradigm

Considering recent trends and developments in medical science, the influence of the multi-stakeholder perspective can be considered to be a paradigm shift in science and its relationship to society and policies that occurred in the second half of the twentieth century, with major implications for health, industry, drug development, the market, and society in relation to internationalization and globalization. Our current discussion on novel applications of BC and putting these into practice through different stakeholder initiatives as an innovative biomaterial is intertwined with that shift. New opportunities and also new challenges arise and the power of MSIs furthermore moves science, policy, business, and society, including SMEs and public and private investors (health, industrial, and civil sector), forward regarding the application of innovative biomaterials in bone tissue engineering for promoting innovative, modern, active capability-oriented and commercially exploitable biomaterials. The core process model of MSIs (Fig. 5) attempts to show how social enterprises (SEs) have been formed from social initiatives in order to fulfil their demands by solving communities' concrete social problems, which leads to entrepreneurial spirit and corporate social responsibility through business ethics. This core process model of MSIs is based on the amalgamation of the five Es –

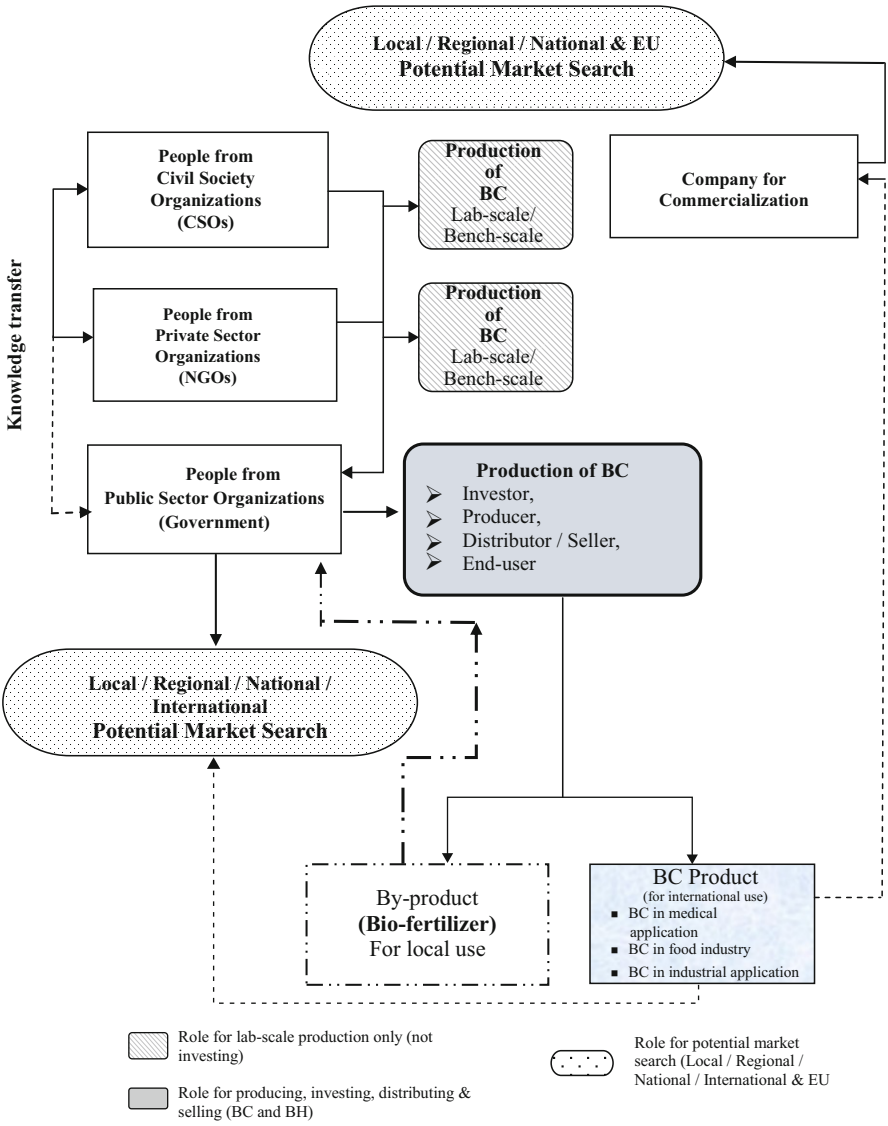

Fig. 4 SMART flow chart of multi-stakeholders' individual role in bacterial cellulose (BC) production from agro-biological resources

effectiveness, explanation, efficiency, entrepreneurial, and ethics – and the five Cs – collaboration, connection, cooperation, competitiveness, and continuity – which promote stability among the different levels, sectors, and types of groups.

On the other hand, the concept of MSIs also covers different phases in multi-stakeholder processes from multi-stakeholder dialogues in an initial norm-setting-up phase to long-established strategic planning, implementing and managing, learning

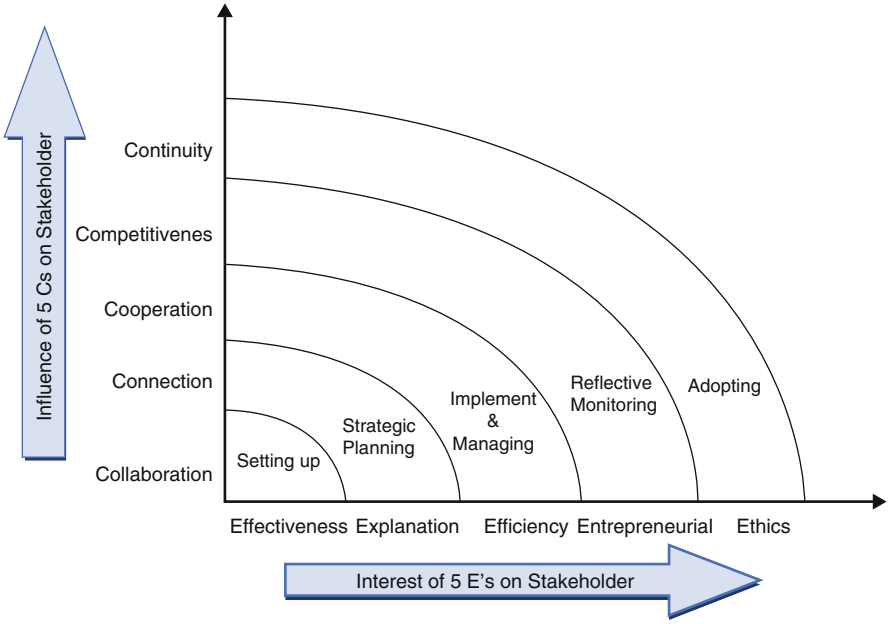

Fig. 5 The core process model of multi-stakeholder initiatives' impact [8]

through reflective practice and monitoring, and learning through adaptive planning that enhances institutionalized initiatives. Therefore, MSIs can be understood as global institutions that include the main corporations and CSOs and are considered to be one type of private regulatory mechanism that tries to fill the governance gap by involving corporations, CSOs, and sometimes other actors such as governments and academia or unions to cope with social and environmental challenges across industries on a global scale [46]. As a new form of global governance with the potential to elevate multilateral norms and local actions, multi-stakeholder partnership networks have been characterized by drawing on a number of different actors in civil society, government, and business [47]. Accordingly, the MSI process takes a view in which every stakeholder will be involved in the development process and will have a valid vision and relevant knowledge and experience to contribute to the decision-making [48, 49].

In a nutshell, from an innovation paradigm point of view, MSIs can be raised through negotiation processes involving representatives of different business, civil society, and other possible stakeholder groups as well as individuals to address certain sustainability problems. Generally, the focus of interest is on the role of stakeholders, especially in the initial phase of dialogue or negotiation. During the implementation phase, the focus of attention may shift towards capacity building or training/certifying individual, group, and organizational competencies within organizations to facilitate organizational learning. To better comprehend the approach of MSIs, this section familiarized the reader with some common elements and

topography in the patterns and practices of multi-stakeholders' partnerships and platforms for sustainable development. Some distinguishing factors were proposed for successful multi-stakeholder practices for the various applications of BC and BHs and their competencies regarding meeting a range of societal challenges in the public and private sectors to connect business performance and sustainability as well as enriching formal capabilities that enable the key sector for collaboration across transdisciplinary discourse. This deliberately stimulates improvement in public, private, and civil society's knowledge production systems (strengthening stakeholders' skills).

3.2 Challenges of MSIs for Various Applications of BC and BH

MSIs are collaborations between business, civil society, and other stakeholders that seek to address issues of mutual concern and sustainability. In order to achieve this, initiatives may work to facilitate dialogue across stakeholders (science, policy, business, industry SMEs) and groups, foster cross-sector engagement, or develop a strategy and apply standards for corporate or government conduct. The significant stakeholders are basically an association of academic and industrial researchers as well as multi-stakeholders from groups (local, regional, national and international researchers, industrialists, and policy makers) interested in developing both the fundamental and functional research linking the application of BC-based nanocomposites/products in the form of films, foams, and novel materials for various industrial/biomedical applications.

The importance of MSIs will increase the pan-European dimension, by connecting high-quality scientific communities throughout Europe and worldwide (who are working on BC and BHs/biocomposites). Medical research-based companies, policy makers, regulatory bodies, and national decision makers including those in the private sector (i.e., SMEs involved in research on bio-nanocomposites, nanobiomaterials, cellulose-based bio-foam, biofilms, etc.) will provide a key materials platform for the sustainable production of renewable, recyclable, and environmentally preferable goods and products to meet the needs of consumers on a global scale. The challenges of MSIs for application of BC and BC-based products will bring together a critical mass of nanotechnologists, biotechnologists, microbiologists, fiber technologists, polymer scientists, and chemists to determine approaches for both the collective advancement of knowledge and the training of a young generation interested in this field of NBS research. Spreading excellence and widening the dissemination of applications of BC-based products through MSIs is depicted in Fig. 6.

In the context of this issue, it should be highlighted that over the last two decades MSIs have been established in almost every major global industry due to their active participation and responsibility for certifying the production of various innovative eco-friendly products such as BH or BC-based food (Nata Company, Philippines), monitoring the extraction of these nature-based products, and establishing codes of conduct for companies (SMEs) regarding privacy and freedom of expression, amongst other activities. It shows the significance of MSIs, as they measured the

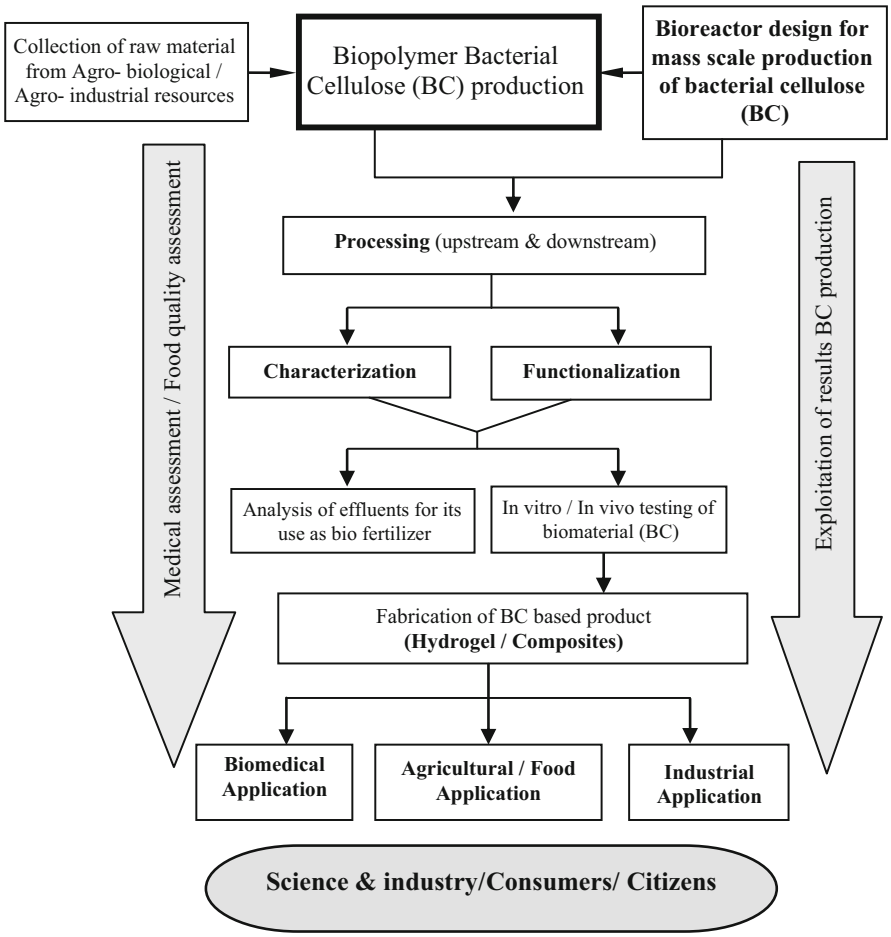

Fig. 6 Multi-stakeholders' challenges in the dissemination and exploitation of various applications of bacterial cellulose (BC)-based hydrogels (BHs)

key challenges that seek to address pressure on agro-biological resources and environmental degradation of social impacts, which have a major direct effect on human well-being. In order to tackle the divergence condition, the most relevant stakeholders (academia and business, science and industry/consumers/citizens) always try to quantify certain key performance indicators (KPIs), such as the following:

- Identification of nature-based product (BC) users' needs;
- Clarification of a market-oriented EU research and innovation agenda for NBS;
- Improved coordination among EU member states, and international research, innovation, and demonstration activities for NBS; and
- Calculate improved cooperation and synergies with relevant strategic international research partners.

In relation to Fig. 6, it is understandable that the distribution plan for the involvement of industry (food/healthcare/others) is a realistic approach that provides a clear plan to encompass the MSIs. From the technological development point of view, the primary aim of the MSI is to improve the environmental performance of the whole supply chain and information, as well as building the capacity of BC production.

3.3 MSIs Influencing the Application of BH for Sustainable Development

The potential contribution of the MSI strategy and its distinguishing features could be in the advantages for organizations' (CSOs, NGOs, and government) capacity enhancement and business development through several stages, phases, and processes. This section highlights the way MSIs can influence the sustainable development of BC and BH applications to meet societal challenges by setting up dialogue through collaboration (increasing effectiveness); planning strategically with mutual cooperation (valid explanation); implementing and monitoring through network and international connections (utilizing resources efficiently); enhancing organizational learning through thoughtful monitoring in order to develop competitiveness (entrepreneurial spirit); and developing learning capability through adopting continuity (growing corporate social responsibility, i.e., business ethics). It is assumed that the social evolution and ecological and economic issues related to sustainable development discussed in the literature on the multi-stakeholder's approach (based on the opinion of the different national and international scholars, academics, policy makers, and researchers) have generally given a comparative overview of the conceptual aspects of MSIs. Investigation shows that the key priorities of multi-stakeholders have a significant impact on local, regional, national, and global success (which influences functional and psychological benefits that create value, i.e., competitiveness), as described in Fig. 7.

Concerning the issue of MSIs for sustainable development of BC-based product applications, their use mainly depends on the planning and adaptive management policy and strategy of the MSP. MSIs also provide opportunity, as well as demonstrating performance and informing the design of new interventions. The thematic model demonstrates that MSIs are the key sector for collaboration across transdisciplinary discourse, which inspires knowledge production system improvement (strengthening stakeholders' skills) in public, private, and civil societies. The model also shows that the linking and networking proficiency of firms, and individuals as well as the government develops through the amalgamation of different groups that raise awareness of innovative biomaterials applications, bringing biotechnologists, material scientists, microbiologists, pharmacists, and service providers together through mutual understanding, strategically planning, defining and analyzing the sustainability problems of BC and BH application, building environmental accountability capabilities, and collaboration.

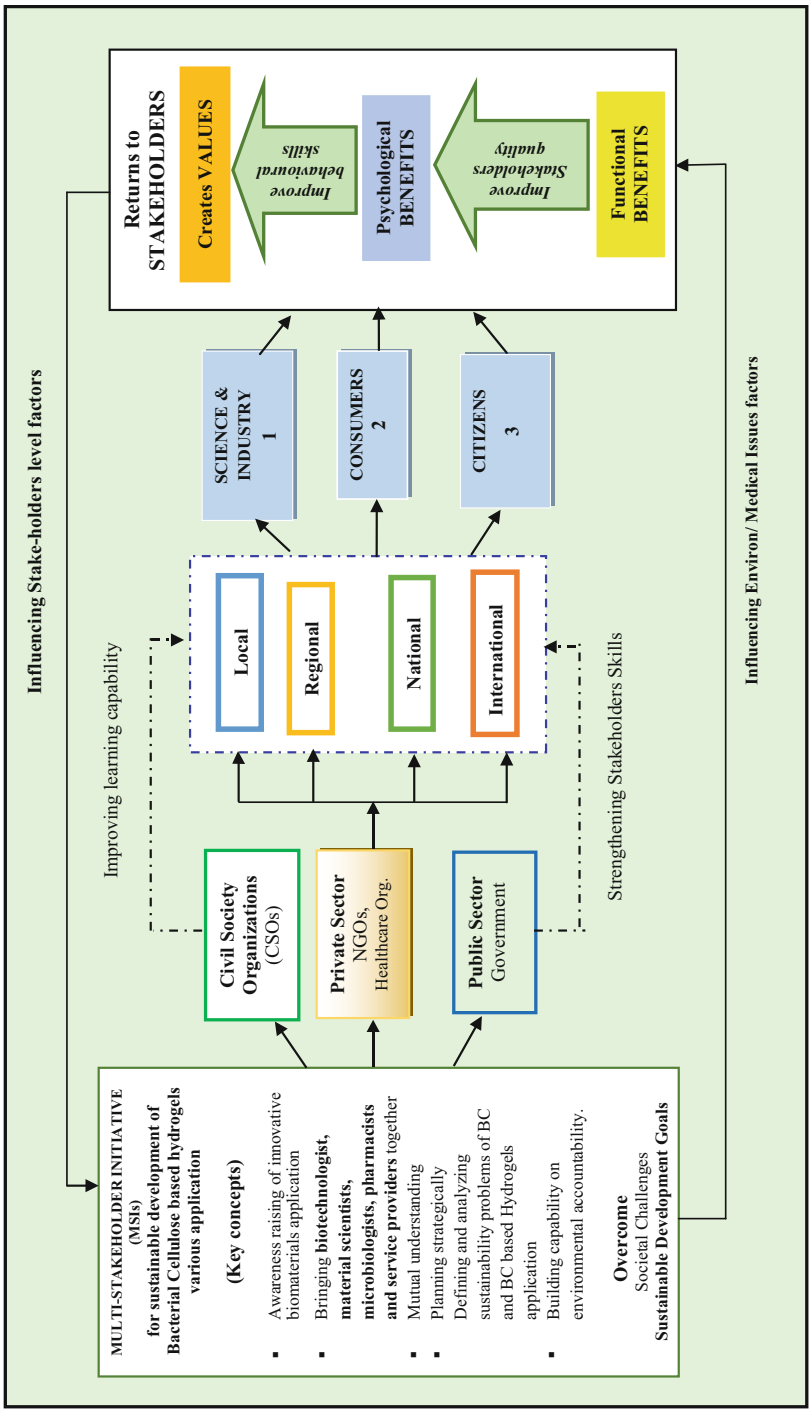

Fig. 7 Thematic model of multi-stakeholder initiatives influencing application of bacterial cellulose (BC)-based hydrogels for sustainable development

Figure 7 shows that stakeholders' initiatives and their governance encourage entrepreneurial learning and strengthen the entrepreneurial spirit relating to specialized technical and administrative skills (i.e., influencing health, agro-food, and industrial sectors). It shows that MSIs (CSO, NGO, and government initiatives) influence and focus on improving stakeholder's behavioral skills, to improve collaboration across scientific, industrial, and clinical communities (i.e., influencing stakeholders' levels of input).

In short, it can be said that the MSI approach could be a powerful instrument for, or even be key to, fostering SDGs in BC and BH production that empower improvements in the different sectors (medical equipment and device manufacturers and potential entrants, regeneration device dealers, distributors and service providers, healthcare service providers, private research institutes, government authorities, and public service boards), research institutes, associations, and academics (levels and types of collaboration due to the presence of organizational learning attributes and priorities that complement community participation). An advantage of MSIs is the reinforcement of internal and external stakeholder's quality in their behavioral outcomes (i.e., individual, group, and institutional competence) of business by improving learning capabilities (i.e., individual, group, and community learning), which leads to promotion of innovative capability and business growth due to their inherent competency.

4 Conclusion

This chapter delivers a brief overview of the MSI approach and the initiative for sustainable development of biopolymers/BC in the field of BC, BC-based biocomposites, biopolymer-based hydrogels, modified or functionalized biopolymer hydrogels, and composite materials that can be produced from agro-biological waste/filtrates. An important aspect lies in the current lack of governance setup for the sustainable development of these innovative biomaterials products, which has not yet been taken into account by most industries. However, natural hydrogels are in demand by biomedical, agro-food, and industrial science. Moreover, industrial scientists perform their R&D work with a commercial focus in fields such as agriculture, food science, environmental science, earth science, pharmaceutical science, engineering, and technology, especially for developing a consensus in today's globalized world. Therefore, the significance of multi-stakeholder representation has gained recognition in a global economy in which major environmental accountability is gaining importance for corporations. While businesses are free to conduct their affairs transnationally, that can create a governance gap. To accomplish the sustainability of various applications of BH, it is essential to emphasize the recent appearance of the concept of MSIs as well as the significance of the social and economic environment spreading across the world, particularly in developing countries such as South-East Asia and Africa and via the G20 countries and the European Development Bank.

In today's dynamic, ever-changing world, there is certainly a rise in self-motivated action that has great influence on the government and economic spheres and CSOs in order to tackle the enormous consequences of changes wherein social, political, and economic change can be brought about. In this sphere of influence, nothing is actually powerful, but each and every person has the power to partially challenge the actions to which they are opposed. In short, this is what we call progress, particularly in relation to sustainable development that supports our social capacity to be able to constructively engage with each other. Basically, to understand the new perspectives, different challenges are necessary to question, stimulate, and take initiative for changing the old conventions, patterns, and values. To move forward requires a creative, responsive, and adaptive outlook.

Thus, organizational learning and innovation strategy has become dominant in recent times. Consequently, the MSI and MSP approach recognizes that the greatest and most multi-faceted problems will never be solved by one group/entity. Hence, the significance of the MSI approach as the only option to bring scientific, community, farmer, environmentalist, economic, policy, and governmental perspectives together to initiate change. The MSI approach enables different perspectives from different communities such as CSOs and NGOs to plug up the governance gap that emerges when state actors are unable or unwilling to ensure the full protection and promotion of ecological responsibility for their citizens. Moreover, MSIs are frequently perceived as more legitimate regulatory tools than other industry initiatives or public–private partnerships because of their purported inclusion of civil society stakeholders in the initiative's governance, implementation, and/or decision-making process.

5 Future Scope

In the current policy discourse, the philosophy of involving multiple stakeholder groups in medical science for R&D in biomaterials fields and resource management as well as for treatments based on regenerative medicine seems overwhelming. Consequently, progressive innovation in biomaterials has trended sharply upward and is expected to double by 2020, especially with a focus in application of bone tissue engineering. Studying a phenomenon such as multi-stakeholder dialogue, a unique thought, had not previously caught many researcher's attention. However, the EU multi-stakeholder innovation platform is now gaining prominence in the EU's policy addressing socio-economic challenges, owing to its part in the forthcoming new program of Horizon 2020. In addition, over the past two decades, innovative biomaterials (BHs) applications have been viewed as a substantial area of research in the field of regenerative medicine.

From the global raw materials governance and dilogue benefit point of view, innovative biomaterial products such as BC and BC-based biocomposites will try to cover economically important raw materials through guidelines from international associations such as G20, the European Development Bank, and those in South East Asia and Africa. Consequently, it can be expected that a more balanced situation in

the world trade market for raw materials will be available that will eliminate the barriers to trade internationally. Therefore, this MSI for sustainable development of various applications of BH will have the potential to benefit economic stability, especially in the high-technology sectors.

The future scope of this work will focus on investigation of the commercialization of natural polymers/biopolymers/innovative biomaterial-based products to address the need to utilize these BHs that could have potential and novel biomaterial applications. As the prevalence of business-related violations of NBS has gained increasing public attention, there has been more and more demand to prevent and remedy these violations. International and domestic law has been seen to largely fail to address the full range of negative impacts of business, driving many actors to work directly with companies to prevent or mitigate such harm through voluntary compliance initiatives, such as MSIs.

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Antimicrobial Food Pads Containing Bacterial Cellulose and Polysaccharides

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Contents

Abstract

Antimicrobial food packaging is one of the major innovations in the field of packaging technology. To extend food shelf life and to contribute to the consumer's health are the main challenges of the new technology. Absorbent pads are

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widely used in food industry in order to preserve sensorial characteristics of packaged fresh or refrigerated food products, such as meat or poultry and also fruit and vegetables which could generate exudates during storage time. Cellulose and cellulose-derived materials are already used as components in food pads architecture. To tailor an antimicrobial food pad using natural antimicrobial agents is also a challenge which could be achieved. The aim of this chapter is to give an overview of antimicrobial packaging, underlying especially the role of natural antimicrobial agents and biopolymers. Examples are focused on cellulose and its derivative uses. In the second part of this chapter, we propose new composite hydrogels composed of bacterial cellulose and other polysaccharides as xanthan and carboxymethylcellulose, hydrogels which could act as super-absorbent of moisture and fluids exuded from packaged fresh food products. As antimicrobial substances we have tested potassium sorbate and thyme essential oil. The samples impregnated with thyme essential oil were tested against four microbial strains: *Escherichia coli*, *Bacillus subtilis*, *Candida utilis (Torula)*, and *Penicillium hirsutum*.

Keywords
Antimicrobial · Food pad · Bacterial cellulose · Carboxymethylcellulose · Xanthan · Moisture absorber

1 Introduction

Active packaging is defined as a packaging containing particular components in or on either the packaging material or in the package headspace with the aim to extend shelf life of food and, at the same time, maintain the food quality. An important class of active packaging is antimicrobial packaging. Its role is to inhibit or to retard the growth of the microorganisms by releasing antimicrobial (AM) agents into the food surface. Many substances were tested as antimicrobial agents. The antimicrobial compounds could be either chemically synthesized or natural ones. They could act by diffusion if they are nonvolatile or as released vapors in the headspace of the packaging, if they are volatile substances. Due to the consumers' concern regarding pollution caused by synthetic substances and especially by synthetic polymers used as packaging materials, the recent trend in the field of antimicrobial packaging is to use natural antimicrobial compounds and biodegradable polymers. Food industry already uses antimicrobial substances to extend shelf life of many products including meat, poultry, cheese, bread, fruit, and vegetables. The incorporation of antimicrobial agents in food is not agreed by consumers, and for this reason the preservative agents must be applied to packaging; therefore developing antimicrobial packaging becomes a necessity. This kind of packaging is more easily accepted by consumers because of their refusal of products containing additives for preservation [1].

Antimicrobial packaging could be used for meat products to minimize the risk of poisoning and spoilage. This industry already uses different preservative systems meant to avoid microbial contamination of meat surface.

For many food products, the main problem is not only the microbial contamination but also the moisture and the fluids exuded by meat, poultry, and fish which are a major cause of food spoilage. These unsanitary juices could be removed by using absorbent pads, sheets, and blankets. For chilled fish large sheets and blankets are recommended, because melted ice must be absorbed [2]. In order to avoid the food contamination by the absorbed juices, antimicrobial moisture regulators have also become a necessity.

This chapter is structured into two parts; the first one is a brief overview of the principles of antimicrobial packaging, especially about antimicrobial food pads. The second one presents experimental work of obtaining and characterization of a new antimicrobial food pad fully biodegradable containing xanthan, carboxymethylcellulose, and bacterial cellulose.

2 Antimicrobial Agents

2.1 Chemically Synthesized Antimicrobial Agents

The first AM agents used for antimicrobial packaging were synthetic, namely, sorbic and benzoic acid and their salts. A very well-known paper belongs to Han and Flores, who examined the mechanism controlling the release of potassium sorbate through various plastic films, in order to obtain an active packaging material [3]. Not only the aforementioned acids and their salts but also other organic acids and their salts are still used as antimicrobial agents (acetic, benzoic, propionic lactic, citric, and malic acids) [4–8]. As matrices in which these organic substances were incorporated, we could mention synthetic polymers like low-density polyethylene, EVA (ethylene-vinyl acetate), and other polyolefins, as well as biopolymers like chitosan, cellulose and cellulose derivatives, soy protein, corn zein, wheat gluten, and gelatine [9–15].

2.2 Nanoparticles Used as Antimicrobial Agents

As a consequence of the growing interest in the field of nanotechnology, a great number of nanoparticles have been used as antimicrobial agents. As nanoparticles there were tested silver nanoparticles (AgNP), titanium dioxide (TiO_2), zinc oxide (ZnO), cuprum oxide (CuO), and magnesium oxide (MgO) [16]. The use of AgNP-loaded packaging materials against microbial growth in foods is very well documented. The AgNPs could be synthesized <ex situ> and <in situ>. In the first approach, the AgNPs are first synthesized and then dispersed into a polymer or biopolymer matrix. In the second approach, the AgNPs are generated starting from precursors in the polymer solution or dispersion. AgNP-loaded materials have been proven effective against different kinds of microorganisms, especially bacteria, even if the acting mechanism of silver particles is not completely understood. Even if research in this field is developing, recently a general concern has been expressed among the scientific community with regard to the risk of exposure to nanoparticles which are present in food packaging and could interact with the human organism [16].

2.3 Natural Antimicrobial Agents

The recent trend in the field of antimicrobial packaging is the use of antimicrobial compounds of different origins: vegetal, animal, or obtained from microorganisms. In the first category, one could include essential oils and other plant extracts which have not only antimicrobial properties but also antioxidants ones. Some nanoclays or layered silicates are also antimicrobial agents but of mineral origin.

2.3.1 Essential Oils and Plant Extracts

Plants are a great source of biomolecules which work in synergism, conferring advantages for plants' survival. Essential oils and other plant extracts are already known for their great antimicrobial and antioxidant potential. They represent secondary metabolites synthesized by plants for their defense against different stress factors. There are several methods for extracting these valuable compounds, namely, steam distillation (especially for essential oils), solid-liquid extraction, and new techniques for extraction enhancement like ultrasound-assisted extraction, accelerated solvent extraction, microwave-assisted extraction, and supercritical fluid extraction. The strong antimicrobial effects of plant extracts are due to their composition, which contains phenolic components (ca. 85%). Phenolic components constitute a major class of secondary metabolites produced by plants. More than 8000 phenolic structures were already identified [17]. These compounds are considered to be essential to the physiology and the cellular metabolism of plants and promote physiological survival of the plant, providing protection against pathogens and predators [18]. From the large class of phenolic compounds, there could be mentioned other subclasses of compounds with antimicrobial and antioxidant properties like flavonoids, phenolic acids, and lignans [19]. The most important members of flavonoids are the flavonols, flavanols, flavones, isoflavones, anthocyanidins or anthocyanins, and flavanones [18]. The antimicrobial and antioxidant effects of phenolic compounds against different pathogenic microorganisms are very well documented [18–20].

Essential oils (EOs) are aromatic oily liquids obtained from different parts of plants. They can be obtained using different methods, steam distillation being the most common in what commercial products are concerned. A great number of EOs is known, but only 300 of them are commercially relevant, especially those destined for flavor and fragrance market or for pharmaceutical applications [21]. They have a complex composition dominated by terpenoids, which are responsible for the flavor and antibacterial properties of EOs [22]. EOs also contain phenolic compounds, low molecular weight aliphatic hydrocarbons, aliphatic alcohols, aldehydes, ketones, acids, acyclic esters, or lactones [23]. In some cases, the antibacterial properties are due to a synergistic effect obtained also with the contribution of other minor components. Some examples are *Salvia officinalis*, certain species of *Thymus* and *Oregano* [21].

Many essential oils were also studied for their antibacterial properties, especially in relation with food, and this trend is continuing due to the consumers' interest for

products' safety with no synthetic additives used for preservation. The majority of essential oils and plant extracts are recognized as safe for commercial applications.

Many experimental studies have demonstrated that essential oils from oregano, thyme, basil, sage, rosemary, clove, coriander, caraway, fennel, nutmeg, pepper, cardamom, garlic, and onion exhibit antimicrobial activities against food-borne pathogenic bacteria [24].

The only problems are associated, on one hand, with the oils' flavors, which are sometimes not tolerated by consumers' taste, and on the other hand with their limit concentrations for the maximum antimicrobial effect desired, especially when these substances are applied directly on the food surface. For this reason, many essential oils are now incorporated in packaging materials in order to have a controlled release of the antimicrobial agents.

2.3.2 Antimicrobials of Animal Origin

There are numerous antimicrobial systems of animal origin, which act as defensive agents against a wide range of microorganisms. Very well documented is chitosan, which is also a biopolymer. Other antimicrobial agents of animal origin are lactoferrin, lactoperoxidase, lysosome, pleurocidin, defensins, histatins, and cathelicidins [24]. There are also lipids of animal origin with antimicrobial activity [23].

Chitosan, which is a deacetylated chitin derivative, is one of the most studied biopolymers which exhibit antimicrobial activity against a large number of microorganisms, being a nontoxic biopolymer [25]. It is already reported that the antibacterial activity of chitosan and chitosan oligomers is dependent on their molecular weight [26, 27]. Foster and Butt have demonstrated in a recent paper that only chitosan solutions have a strong bactericidal activity against a range of medically important bacteria, and one should note that the idea of antibacterial activity of chitosan films is an important misconception [28]. Yeasts and molds form the group that is the most sensitive to chitosan, and they are followed by Gram-positive and Gram-negative bacteria [24].

Various methods are used to prepare chitosan films, the most popular being the casting method [25]. Modern methods used to obtain chitosan composite films with other biopolymers are supercritical carbon dioxide treatment (chitosan/starch film), microwave treatment (chitosan/potato starch film) [29], and electronic beam irradiation [30]. Many essential oils and other antimicrobial substances were entrapped in chitosan or chitosan composite films used for food preservation.

Chitosan/cinnamon oil and chitosan/thyme oil films were used for preservation of refrigerated rainbow trout and chicken products [31]. The results were very promising, the coating film of chitosan with cinnamon oil being able to extend the shelf life during the refrigerated storage of fish samples. Antimicrobial films were prepared by incorporating in chitosan matrix acetic and propionic acid, with or without addition of lauric acid or cinnamaldehyde, these films being used for preservation of meat products: bologna, regular cooked ham, or pastrami [32]. Antimicrobial edible films of chitosan containing garlic oil, potassium sorbate, and nisin were tested against food pathogenic bacteria. The most promising was the film with garlic oil,

with the mention that it could be used only for food where the flavor of garlic oil is not a problem [33].

2.3.3 Antimicrobials Produced by Microorganisms

Bacteria are producing many compounds with antimicrobial properties in order to defend themselves against other bacteria by creating an unfavorable environment to other microorganisms. Bacteriocins can tolerate diverse treatments, such as boiling during pasteurization and sterilization of food, without losing much of their antimicrobial activity [24]. Bacteriocins are considered natural products because they are presented in fermented or non-fermented food from ancient times [34]. A large class of bacteriocins has been isolated from lactic acid bacteria, the most important members being nisin and pediocin, which are widely used for food preservation [34]. Nisin belongs to the lantibiotic class of bacteriocins, cationic and hydrophobic peptide [35]. Nisin has an antimicrobial activity directed primarily against Gram-positive bacteria and in particular against the spore forming ones [36–38]. Pediocins are effective against many strains of sublethally stressed Gram-positive and Gram-negative bacteria [35].

2.3.4 Nanoclays

Nanoclays are layers of silicate clay minerals composed of nanoplatelets with nanometric thickness. The most well-known of this class of minerals are montmorillonites (MMT), hectorite, and saponite. The incorporation of nanoclays in polymer composites has the aim to enhance polymer mechanical and barrier properties. Because many natural nanoclays are hydrophilic and cannot be used to obtain nanocomposites with hydrophobic polymers, they are chemically modified. In order to replace the inorganic cations with organic surfactants, which intercalate into the clay gallery, cation-exchange reactions are used [16]. Hong and Rhim (2008) have tested the antimicrobial activity against four representative pathogenic bacteria of three kinds of commercially available montmorillonite nanoclays. The first was a naturally occurring one (Cloisite Na^+), and the others were organically modified (Cloisite 20A and Cloisite 30B). From the tested nanoclays, Cloisite 30B performed the best bactericidal effect against Gram-positive species and a remarkable bacteriostatic effect against Gram-negative organisms [39]. Cloisite® 10A, a modified montmorillonite with quaternary ammonium salt (organo-Mt), and Cloisite® Na^+ as natural montmorillonite were tested against *E. coli* (ATCC 25922) and *S. aureus* (ATCC 6538) for textile applications. From the two nanoclays tested, organo-Mt modified with ammonium quaternary salt showed better antimicrobial properties compared to natural montmorillonite [40]. Enhanced antimicrobial activity was measured in composites of nanoclays naturally and organically modified with different biopolymers and especially chitosan. Chitosan-based nanocomposite films were prepared by Rhim et al. using an unmodified montmorillonite (Na-MMT) and an organically modified montmorillonite (Cloisite® 30B). Cloisite 30B-incorporated film showed a higher antimicrobial activity against *S. aureus* and *L. monocytogenes* than Na-MMT-incorporated film [41]. Other examples of antimicrobial activity of nanoclays combined with chitosan are given by Azeredo et al. [16].

Nanoclays combined with silver nanoparticles and copper exhibit also antimicrobial activity in powder form or incorporated in different polymer matrices (agar, zein, polycaprolactone, calcium alginate) [16, 42]. Nanoclays could have an indirect antimicrobial activity by controlling the diffusion or by enhancing the retention of other AM agents in polymer matrices [16].

3 Biopolymers Used in Food Packaging

The market of packaging materials is still being dominated by synthetic polymers that exhibit a great number of advantageous characteristics in terms of transparency, softness, mechanical resistance, heat sealability, and transfer properties. Being produced in very high quantities, they are generally available at low prices. Two are the main concerns for the future of plastics: one of them regards the depletion of natural oil resources (feedstock for synthetic polymers), and the second comes from the environmental pollution due to the lack of biodegradability of these materials. The alternative is represented by biodegradable polymers. These are investigated by many researchers, and some biopolymers are already commercially available. It is estimated that the production capacity of biobased polymers will reach nearly 12 million tons by 2020 [43].

Biopolymers could be natural ones, being extracted from renewable resources such as polysaccharides (cellulose, starch, chitosan, chitin, guar gum, alginate, carrageenan, pectin) and proteins (soy proteins, caseinates, gluten, zein) and synthetic ones which are obtained from oil-based monomers (polycaprolactones (PCL), poly(vinyl alcohol) (PVA), ethylene-vinyl alcohol (EVA) copolymers, polyesteramides (PEA)); there are also synthesized biopolymers from monomers obtained by fermentation (polylactic acid (PLA)) or obtained by microbial fermentation (polyhydroxyalkanoates (PHAs), bacterial cellulose, xanthan gum, and gellan). One of the problems associated with the use of biopolymers in food packaging applications is the difficulty of processing them in conventional equipment due to their poor mechanical properties. Some of the biopolymers are hydrophilic, and their low water resistance also limits their use as packaging materials. Generally speaking, their transport properties are sometimes inferior to those of synthetic polymers. Finally, their price is still high. Many of them are used in edible films and coating [44].

In order to obtain antimicrobial food pads, three biopolymers were used in the experimental part, these being bacterial cellulose (BC), carboxymethylcellulose (CMC), and xanthan gum (XG). For these biopolymers a brief presentation will be done to justify their use.

3.1 Bacterial Cellulose

Cellulose, which is the most abundant renewable organic material produced in the biosphere, serves as the dominant reinforcing phase in plant structures. The main

sources for cellulose are wood or annual plants (e.g., cotton, hemp, linen, jute, flax, kenaf, ramie). In plants, cellulose is only a part of lignocellulosic material together with hemicellulose and lignin, and these components need to be separated. Cellulose is generally extracted by using one of the two methods, sulfite or by pre-hydrolysis kraft pulping (sulfate method). The kraft pulping method is the most popular and is responsible for around 80% of the world cellulose production. All the cellulose purification processes at industrial scale are high energy consumers, approximately 1000 kWh/ton, which represents still a high and expensive industrial activity [45]. Nowadays, green chemistry is also used to extract valuable wood components, but these attempts have only been tested at laboratory scale [46]. Even if wood and annual plants are recognized as the major source of cellulose, however, there are only a few microorganisms (bacteria, algae, tunicates, or fungi) which produce certain amounts of extracellular cellulose, known as microbial cellulose (MC) [47]. Cellulose produced by different bacteria strains was named bacterial cellulose (BC). Bacterial cellulose is one of the most promising biopolymers, being of great importance in the medical field as well as in many industrial areas. Bacterial cellulose is produced in different fermentation media, mainly by the acetic acid bacteria, which are members of the *Acetobacteraceae* family and particularly belong to the genera *Komagataeibacter* (classified first as *Acetobacter* and later as *Gluconacetobacter* genus) [45]. Bacterial cellulose is composed of (1→4)-β-glycosidic-linked glucose units. These linear glucan chains form highly regular intra- and intermolecular hydrogen bonds which confer to BC a high water affinity and other interesting properties. Bacterial cellulose (BC) is chemically identical to plant cellulose (PC) but possesses a different macromolecular structure and physical properties which give it special features, which are not encountered in cellulose obtained from plants. For example, both biopolymers have high crystallinity (usually in the range 40–60% for plant cellulose and above 70% for BC), and both are insoluble in water and other common solvents. Fibrils of BC are 100 times thinner than that of plant cellulose, making its structure more porous. The unique nanofibrillar structure of bacterial cellulose determines its potential application in the medical field, including potential scaffold for cartilage tissue engineering, wound dressing, and drug delivery systems [48–51]. For the present chapter, we have in view bacterial cellulose's food applications. BC being pure cellulose, it could be used as dietary fiber and was recognized as safe (GRAS-generally recognized as safe) in 1992 in the USA [52]. A bacterial cellulose gel is consumed in the Philippines under the commercial name of nata as a low-calorie dessert. It is considered a dietary and healthy food. Its name could be completed with the carbon source of the fermentation medium: nata de coco is obtained from coconut, and nata de pina is obtained from pineapple [53]. BC could be also used to modify the rheology of food, being a thickening, gelling, stabilizing, emulsifying, and water-binding agent [52, 53]. BC was used in vegetarian meat in combination with *Monascus* extract to give the red color of the final product [52]. Food products containing BC could be consumed also for a low-cholesterol diet.

BC could as well be used in order to obtain food packaging materials in three ways: as pure material, as chemically modified, and, in most of the cases, as reinforcing material in composites with other polymers and biopolymers. In the first case, the BC's use as food packaging is not economically feasible due to its high price. The possibility to use BC in biomedical applications like artificial skin, artificial blood vessels, artificial cornea, heart valve, wound dressing material, and artificial bone (especially as BC-hydroxyapatite composite) are more important, and the products are of high value [54]. The only feasible application of BC as pure material could be in document restoration. Santos et al. have tested lining papers with bacterial cellulose sheets [55]. The use of BC as reinforcing material may offer advantages for specific conservation treatments in comparison with other materials [55]. The conclusion of these studies was that BC may improve the physical properties of the damaged paper and could be a promising material for the restoration of paper documents [56]. The barrier properties of BC modified by controlled heterogeneous esterification with hexanoyl chloride were also studied for different applications of BC in the packaging industry [57]. BC-calcium carbonate composites were obtained in different conditions with possible applications for paper manufacturing [58, 59]. For meat, antimicrobial packaging BC containing nisin was used. The active BC films have produced the decline of *L. monocytogenes* populations on frankfurters, proving themselves as promising materials for antimicrobial meat packaging [60]. Functionalized films BC-lactoferrin were prepared as edible antimicrobial packaging, being used especially for fresh sausage as a model of meat products [61].

Due to its special properties, BC has been used in the preparation of a great number of composite materials with various applications. Having a high hydrophilicity, BC could be used to obtain composite materials with many biodegradable polymers. Among them, poly(vinyl alcohol) (PVA) is a very good candidate.

Composites PVA-BC with antimicrobial properties were prepared by our research team in order to be used as active food packaging materials. BC was used either as wet powder, or as wet fibrils, and was dispersed in PVA aqueous solutions. Sorbic acid was used as antimicrobial agent [4, 62, 63]. Sorbic acid release was studied from PVA-BC composites from monolayer films and from multilayer films. The multilayer films were obtained using also wet BC sheet as cover layers. The antimicrobial effect of PVA-BC composites containing also sorbic acid was tested against *Escherichia coli* K12-MG1655, which indicated that the new composites possess antimicrobial properties and could be used to obtain antimicrobial food packaging [64]. The antimicrobial activity was obtained also for composite PVA-BC containing sorbic acid, BC being dispersed as wet fibrils in PVA solutions. The designed film showed antibacterial effect against *Escherichia coli* and could be also considered a promising candidate for obtaining food antimicrobial packaging [62].

BC-silver composites that were reported especially for wound dressing applications could also be used for obtaining food packaging materials [65–68].

3.2 Carboxymethylcellulose

Carboxymethylcellulose (CMC) is a commercially available water-soluble cellulose ether of major interest in the hydrogel synthesis and for food packaging applications besides hydroxypropyl cellulose (HPC), hydroxypropyl methylcellulose (HPMC), and methylcellulose (MC). There are several available types of CMC based on particles' size, degree of substitution, viscosity grades, and hydration characteristics. For general thickening applications, high viscosity grades are chosen for economic reasons, but in film applications, low-viscosity CMC solutions are preferred [69, 70]. CMC is one of the polysaccharides which have been used in edible films and coatings but also for encapsulation purposes. CMC is compatible with a wide range of other food ingredients, like proteins, sugars, starches, and other hydrocolloids [70]. Edible films starch/carboxymethylcellulose (CMC) were prepared by using a casting method. CMC/starch biocomposite films could replace starch films, since they have better physical and mechanical properties than starch films [71]. A hydrogel film containing CMC and polyvinylpyrrolidone was synthesized under controlled environmental conditions. The obtained films are transparent and flexible and show good mechanical properties. Being also biodegradable, they could be used as food packaging material [72]. Superabsorbent hydrogels containing CMC will be presented in another paragraph.

3.3 Xanthan

Xanthan gum is a water-soluble anionic polysaccharide produced by *Xanthomonas campestris*, being a well-known food hydrocolloid. Xanthan is nontoxic and for this reason has been approved by the United States Food and Drug Administration (FDA) as food additive. It is used in food industry as thickener and stabilizer. It has the property to control the rheology of water-based systems, and even at low concentrations, its solution has still a high viscosity. Its aqueous solutions exhibit pseudoplastic properties. Here is a brief enumeration of the roles it can play: as hydrocolloid it is used in bakery product production, as bodying agent in beverages and squashes, in dairy industry as stabilizer of many products, in dressings, for pet food production, syrups, and toppings obtaining [73]. Xanthan has also applications in pharmaceutical, cosmetic, gas, oil, and other industries. For the aim of this paper, we are interested in the films and hydrogels containing xanthan and which could be used in food packaging or as superabsorbent materials. Xanthan hydrogels could be obtained by chemical crosslinking using epichlorohydrin, glutaraldehyde, metabisulfite, citric acid, adipic acidic dihydrazide, or sodium trimetaphosphate to form hydrogels [74, 75]. Hydrogels containing xanthan could be obtained by chemical crosslinking using graft polymerization.

Physical crosslinking can also lead to obtain xanthan hydrogels by freeze thawing, ionotropic gelation, and polyelectrolyte complexation. A physical xanthan gel was obtained by a simple method through incorporation of montmorillonite particles at a critical concentration. The results have indicated that 2.0% w/w of

MTT concentration is sufficient to obtain a consolidated hydrogel [76]. Chitosan and xanthan gum, being polyelectrolyte with opposite charges, they could form polyelectrolyte complex gels [77, 78].

Hydrogels of xanthan crosslinked by esterification reaction at 165 °C, in the absence or in the presence of citric acid, were obtained and characterized. Their swelling behavior was investigated under different medium characteristics, as salt type and pH. Crosslinking of xanthan in the presence of citric acid forms a network with higher crosslinking density and low swelling degree [79, 80]. A superporous hydrogel was synthesized through chemical crosslinking by graft copolymerization of 2-hydroxyethyl methacrylate (HEMA) and acrylic acid (AA) onto xanthan gum (XG) by Gils et al. [81]. The prepared hydrogels have a high swelling degree and de-swelling ability, are biodegradable, and have a low content of residual monomers, being suitable for biomedical applications. Acrylamide was also used in a graft polymerization to synthesize a crosslinked hydrogel containing xanthan [82]. The measured properties of the obtained hydrogel recommend it as a pH and temperature-sensitive smart polymer. Another example of a graft copolymer is the one obtained from *N*-vinyl-2-pyrrolidone and xanthan gum [83].

Interpenetrating polymer network (IPN) hydrogel microspheres of XG and poly (vinyl alcohol) (PVA) were prepared for drug delivery. As model drug ciprofloxacin hydrochloride was used [84].

Organic-inorganic composites superabsorbent xanthan gum-g-poly(acrylic acid)/loess (XG-g-PAA/loess) in aqueous solution were also synthesized. A composite XG-g-PAA/loess containing 2 wt% of loess has a very high swelling ratio in distilled water (maximum 610 g/g) and only 54 g/g in NaCl solution [85].

4 Cellulose-Based Superabsorbent Hydrogels

Superabsorbent polymer (SAP) materials are hydrogels that can absorb and retain water or aqueous solutions up to thousand times of their own dry weight. Due to their excellent hydrophilic properties and high swelling rate, SAPs have been used in many applications, the most well-known being those in the medical area (especially as infant diapers and antibacterial materials) and also in the agricultural field to improve soil water retention and other soil properties. Furthermore, SAPs could be used also as delivery materials for drugs, fertilizers, or other active substances [86–90]. SAPs could be divided into two main classes: synthetic and natural. Most of the superabsorbent materials which are currently in use are produced from acrylic acid (AA) or its salts and from acrylamide (AM), using different polymerization techniques [91, 92]. These crosslinked polymers have a very high swelling degree (1000 g water/g SAP) but also present some drawbacks, because they are non-biodegradable and are obtained from petroleum.

For these reasons, there is a growing interest for developing new SAPs starting with biodegradable polymers such as cellulose and its derivatives, starch, chitin, and chitosan [93–95]. Cellulose and its derivatives (CMC, hydroxypropyl methylcellulose, methylcellulose, and hydroxyethyl cellulose) were used to prepare hydrogels

either using physical or chemical synthesis methods. The most frequently encountered physical methods for obtaining hydrogels are heating-cooling polymer solution, ionic interaction, complex coacervation, H-bonding, and freeze thawing, thoroughly described in many review papers [96, 97]. Not all the specified methods could be used to obtain hydrogels starting from cellulose and its derivatives, and not all the hydrogels obtained are superabsorbent materials. Some examples will be given below.

Aqueous solutions of methyl and hydroxypropyl methylcellulose were used to prepare reversible hydrogels. Gelation of these solutions is due to hydrophobic interaction between molecules containing methoxyl substitution. The degree of substitution of the cellulose ethers and the presence of salts in solution are influencing the sol-gel transition temperature [98, 99]. Li (2002) has prepared also thermoreversible gels starting from aqueous solutions of methylcellulose, the parameters which were varied being methylcellulose concentration and temperature [100]. Thermo-gelation behavior of hydroxypropyl methylcellulose and hydroxyethyl methylcellulose aqueous solutions was investigated by rheology to determine the aggregation temperature and gelling temperature [101, 102]. An interesting idea was to prepare hydrogels of cellulose derivatives based on cryogenic treatment and UV irradiation. In this technique there were used semi-dilute aqueous solutions of different cellulose derivatives, containing photoinitiator, maintained at negative temperatures (−20 °C) and then crosslinked under UV irradiation. The main advantages of these techniques are the simplicity and the extremely short irradiation time required for obtaining high-quality cryogels [103]. Not only cryogels of cellulose derivatives were prepared by using this method but also cryogels based on two biodegradable polymers, one of them being hydroxyethyl cellulose and the other being chitosan. H_2O_2 and *N*,*N*′-methylenebisacrylamide were used as photoinitiator and, respectively, as crosslinking agent [104]. Cellulose/xanthan gum composite films and hydrogels were obtained through gelation with 1-butyl-3-methylimidazolium chloride (BMIMCl), which is an ionic liquid. The cellulose/xanthan gum composite hydrogels were prepared by immersing the ion gels in water. Their water content is very high, more than 90% [105]. Using a mixture between NaOH/urea as cellulose solvent, Chang et al. (2008) have prepared composite hydrogels cellulose/poly(vinyl alcohol) by freeze/thaw, repeating the treatment with and without a chemical crosslinker (epichlorohydrin). Equilibrium swelling degree was higher for the chemical crosslinking samples than the physical hydrogels [106]. The samples prepared by repeating freezing/thawing cycles exhibit a dense structure between cellulose and PVA and in consequence have a high mechanical strength [106]. Thermally sensitive pH-dependent gel containing a cationic polysaccharide (chitosan) and CMC was obtained by physical methods. The polyelectrolyte solutions formed by the two biopolymers remain liquid at physiological pH but turn into gel at body temperature. In the authors' opinion, hydrophobic interactions seem to be the main driving force to form a chitosan gel in the presence of CMC, depending on the working temperature [107].

Chemical synthesis methods are widely used to fabricate cellulose and cellulose derivative-based superabsorbent hydrogels. Chemically crosslinkers such as aldehyde

(e.g., glutaraldehyde, adipic acid dihydrazide), epichlorohydrin, urea derivatives, carbodiimides, and multifunctional carboxylic acids are used for cellulose and its derivatives crosslinking [99]. The crosslinking reactions among the cellulose chains might take place not only in water solution but also in organic solvents. Solvents, such as *N*-methylmorpholine-*N*-oxide (NMMO), ionic liquids (ILs), and alkali/urea (or thiourea) aqueous systems, have been developed to dissolve cellulose, widening the opportunities for the preparation of cellulose hydrogels. These systems are reviewed by Chang and Zhang [108].

Many chemically crosslinker agents are toxic even at low concentrations, and for many applications this could be a serious problem [96, 99]. A green alternative is offered by polycarboxylic acids; in this case the mechanism of crosslinking is condensation reactions between hydroxyl groups of polysaccharides with carboxylic acids [96, 99]. A brief review will be presented by taking into account recently published research papers on this subject.

Cellulose/carboxymethylcellulose (CMC) superabsorbent hydrogels in NaOH/urea aqueous system, using epichlorohydrin as crosslinker, were prepared. In this hydrogel, cellulose molecules act as the strong backbone of the network structure and CMC, which is highly hydrophilic and contributes to the high swelling ratio. The experimental results have proved that the equilibrium swelling ratio could be improved by changing the amount of CMC [93]. Hydrogels were also prepared starting from cellulose and sodium alginate solution and using epichlorohydrin as crosslinker, with the aim to obtain materials with large porous structure. The cellulose solution was prepared using 6 wt% NaOH/4 wt% urea/90 wt% water mixture. The maximum equilibrium swelling ratio which was attained was 253.7 g/g [109]. Cellulose/carboxymethylcellulose (CMC) hydrogels were synthesized using the same solvent mixture for cellulose (NaOH/water/urea) but a nontoxic crosslinker, polyethylene glycol diglycidyl ether (PEGDE). The highest swelling ratio obtained was 230 g/g. In saline solution, the swelling ratio diminished significantly, this being a limiting factor for future applications of the prepared hydrogels [110]. An interesting idea was to prepare superabsorbent hydrogels with antimicrobial properties and good mechanical strength, starting from quaternized cellulose (QC) and native cellulose in NaOH/urea aqueous solution and using epichlorohydrin as crosslinker. The properties of the obtained hydrogels depend very much on the contents of quaternary ammonium groups in hydrogel networks [111].

Chitin/CMC hydrogels were prepared using epichlorohydrin as crosslinker. For chitin solubilization there was used the same mixture as cellulose (8 wt% NaOH/4 wt% urea in water). High swelling ratios were obtained, confirming that the chitin/CMC hydrogels could be considered as superabsorbent hydrogels. The hydrogel with the following composition: 20 g (3 w% chitin solution) and 80 g (3 w% CMC solution), was the most effective in distilled water, having a swelling ratio around 1200 g/g. The swelling degree is increasing with the increase content of CMC [112].

Highly absorbing cellulose-based hydrogels were synthesized by crosslinking carboxymethylcellulose and hydroxyethyl cellulose aqueous solution using divinylsulphone (DVS) or carbodiimide as crosslinking agents [113, 114]. For the samples crosslinked with DVS swelling, the measurement was done in water but

also in ionic solutions and at different pH values. For all the studied samples, an increase of the swelling ratio was measured with the increase of the pH of the external solution [113]. A superabsorbent material with agricultural uses was obtained starting from the same biopolymers carboxymethylcellulose and hydroxyethyl cellulose, citric acid being used as catalyst, and a carbodiimide as crosslinker. A pilot study has confirmed the possibility to use these hydrogels as water reservoir in the cultivation of a "cherry tomato" [115]. Hydroxypropyl methylcellulose (HPMC) was crosslinked with citric acid (CA) and sodium dihydrogenophosphate (NaH_2PO_4) being used as catalyst. The obtained films were tested for their moisture resistance in order to be used as packaging materials [116]. Two cellulose derivatives, namely, sodium carboxymethylcellulose (CMCNa) and hydroxyethyl cellulose (HEC), were used for hydrogel preparation using citric acid as crosslinker. Citric acid concentration was varied between 10% and 20% (w/w polymer). Hydrogels with high swelling degree were obtained with a reduced concentration of citric acid. For a hydrogel containing CMCNa/HEC weight ratio 3/1 mixture with 3.75% w/w CA, a swelling degree of 900 g/g was measured. The proposed reaction mechanism is an esterification one, being based on an anhydride intermediate formation. The obtained materials were destined to be used as superabsorbents in agriculture [117]. Not only citric acid was used as crosslinker but also malic and succinic acids. Hydrogels with antimicrobial properties were prepared using CMC as biopolymer and the aforementioned carboxylic acids as crosslinkers. As antimicrobial particles ZnO_2 were synthesized. The composite hydrogels have a high swelling degree and also a very good antibacterial activity against Gram-positive and Gram-negative bacteria [118].

Not only chemical crosslinkers can be used to obtain superabsorbent hydrogels but also physical treatments (i.e., electron-beam irradiation, gamma irradiation, microwave irradiation during polymerization) [92]. Ibrahim and Salmawi have used CMC and sodium alginate (SA) blends to prepare hydrogels using different gamma rays irradiation doses. The irradiation dose influences the gel fraction and the swelling degree. The obtained hydrogels have also antimicrobial activity [119]. The same biopolymers (CMC/SA) were used to prepare superabsorbents by gamma irradiation. The ability of these hydrogels to adsorb metal ions from wastewater was tested [120]. CMC and polyvinylpyrrolidone were crosslinked with gamma irradiation in order to prepare superabsorbent hydrogels with agricultural uses. As in the previous examples, hydrogels have a good swelling degree, which is greatly affected by their composition and absorbed dose [121]. Superabsorbent gels were prepared by gamma irradiation from aqueous mixtures of carboxymethylcellulose and starch by Fekete et al. [122]. Hydrogels containing 30% starch and prepared at 20 kGy irradiation dose showed the best swelling properties (water uptake of ~350 g water/g gel), especially in an environment with high electrolyte concentration.

Cellulose-based superabsorbents could be synthesized by grafting acrylic acid and other monomers to cellulose or its derivatives. As polymerization methods, the following have been used: aqueous solution polymerization, inverse-phase suspension polymerization, and microwave irradiation polymerization, largely described by Ma et al. [92].

Hydroxyethyl cellulose (HEC)/acrylic acid (AAc) copolymer gels with superabsorbent properties were synthesized from aqueous solutions by radiation-initiated crosslinking [123]. The HEC content was maintained as high as possible for a higher biodegradability of the final product. Effects of acrylic acid ratio, solute concentration, and absorbed dose upon hydrogel properties, and especially upon their swelling degree, were studied [123].

Cellulose and cellulose derivative-inorganic hybrid hydrogels are also in the attention of the researchers due to the fact that materials with high functionality could be developed by incorporation of inorganic particles in the polymer structure.

Cellulose/acrylic polymer/inorganic particle superabsorbent composites were obtained using silicon dioxide (SiO_2) and titanium dioxide (TiO_2). Graft copolymerization of acrylic monomer was used as a method to prepare new superabsorbent composites using cellulose derivatives. For the composites incorporated with different cellulose derivatives, the swelling degree in distilled water and saline solution is the highest for those superabsorbents containing carboxymethylcellulose [124]. Wheat bran, which has a high content of natural cellulose, hemicelluloses, lignin, and protein, was modified by graft copolymerization of acrylic acid and various clays with the aim to prepare nano-hybrid organic-inorganic superabsorbents. The swelling degree is very much influenced by the type of clay used in the superabsorbent preparation. The new composites could be good candidates for agricultural and horticultural applications, their capacity of urea loading being also tested [125]. Graft polymerization of acrylic acid onto hydroxyethyl cellulose was performed in the presence of diatomite clay as nano-filler, *N*,*N*′ methylenebisacrylamide as crosslinker, and ammonium persulfate as initiator. A maximum swelling ratio of 1174.85 g/g was measured in distilled water and 99.55 g/g in a saline solution (0.9 wt% NaCl) [126]. Not only clays but also graphene oxide was used as filler for incorporation in a superabsorbent obtained by graft polymerization of acrylic acid on carboxymethylcellulose backbone. The hybrid superabsorbents with graphene oxide have a higher swelling degree and an enhanced thermal stability in comparison with the copolymer without filler [127].

Interpenetrating polymer network is defined as a blend of two or more polymers in a network with at least one being synthesized and/or crosslinked in the presence of other, without any covalent bonds between them [128]. Many other polysaccharides or their derivatives have been used in the preparation of semi-IPN or IPN composite hydrogels [128]. Interpenetrating polymer network technology has been applied for synthesis of cellulose-based superabsorbents. Many examples of cellulose-based hydrogels which could be considered as interpenetrating polymer networks are given by Chang and Zhang [108].

5 Antimicrobial Food Pads

Moisture absorbers (MA) play a very important role for the extending shelf life of food, as the excess moisture is a major cause of spoilage. MA could be sheets, blankets, and pads [2]. They could be destined to fruit and vegetables but also for

meat, poultry, and fish products. Using MA, the food quality could be maintained by inhibiting microbial growth and avoiding the food degradation because of high water content. Even if the unsanitary juices are absorbed by MA, they could also generate undesirable odors or could lead to food spoilage. For this reason the incorporation of antimicrobial agents into a food pad could solve this problem. As classical desiccants used in the forms of sachets, the following could be mentioned: silica gel, calcium oxide, activated carbon, molecular sieves, and natural clays [129, 130]. They are used for moisture absorption for products like cheese, chips, nuts, candies, peanuts, and spices [2]. Nowadays the architecture of food pads is more complicated. Common absorbent pads include an intermediate layer formed by the absorbent material between two layers of microporous or non-woven polymer [130]. The upper and lower materials could be flexible thermoplastic films or coated cellulosic material. Different combinations of these materials are also in use, being largely described by Otoni et al. [131]. As moisture absorber, many materials like non-woven cellulosic pads, superabsorbent polymers, absorbent gels, and thermoplastic polymer fibers are used. Superabsorbent polymers which were tested as absorbing materials are polyacrylate salts, carboxymethylcellulose (CMC), and graft copolymers of starch [129]. The next step in the evolution of food pads was the incorporation of antimicrobial agents in their composition. Nanoparticles such as silver and cooper were already studied as antimicrobials for food packaging [131–134]. EOs are more promising than antimicrobial substances, being naturally obtained. Among the most tested EOs against food pathogens are *Allium sativum* essence oil, basil, bergamot, clove, cinnamon, coriander, eucalyptus, lemon, lemongrass, oregano, rosemary, sage, thyme, and tea tree [21, 135, 136]. The synergism between different EOs and other substances has also been studied [135]. Combinations of plant extracts could be used also with the aim to minimize concentrations and consequently reduce sensory impact [137]. Very important is also the interaction between essential oils and food ingredients [137]. The use of bacteriophages to control pathogens is also a promising way to reduce microbial risk potential. Because the incorporation of these antimicrobial agents is still not very well-known, Gouvêa et al. have tested a mix of six bacteriophages in meat trays to be used for refrigerated foods [138]. Some commercially available moisture regulators which could be applied to meat products are presented by Ahmed et al. 2017 [130].

6 Synthesis of Carboxymethylcellulose, Xanthan Gum, and Bacterial Cellulose Hydrogels

6.1 Materials

All chemicals are commercially available, being of analytical grade (purchased from Sigma-Aldrich) and used without further purification. All solutions were prepared using high-quality deionized water. For antimicrobial activity measurements, were used three media. The first one is YEPD medium or yeast extract peptone dextrose, also often abbreviated as YPD medium, which is a complete medium for yeast

Table 1 Hydrogel composition

	Samples							
Composition (g)	P1	P2	P3	P4	P5	P6	P7	P8
CMC	1	1	1	1	1	1	1	1
Xanthan gum	–	–	3	3	3	3	6	6
BC (wet gel)	–	2	–	4	–	4	–	2
Citric acid	0.25	0.25	0.6	0.6	0.4	0.4	0.8	0.8

growth. It contains yeast extract, peptone, double-distilled water, and glucose or dextrose. It was used as solid medium by including agar. The second one is PDA medium (potato dextrose agar – a specific medium for the fungi cultivation and estimation of mold population in food industry). For bacterial strains a third medium, Nutrient Agar, was used.

6.2 Hydrogel Preparation

Biocomposite hydrogels containing carboxymethylcellulose (CMC), xanthan gum (XG), and bacterial cellulose (BC) hydrogels were prepared by dissolving CMC and/or xanthan in deionized water together with a certain quantity of citric acid, in order to obtain different ratio between the two components. For the hydrogels containing also bacterial cellulose, this biopolymer was first grinded in wet state and then dispersed in the polymer solution containing CMC and/or CMC-xanthan. The solutions were homogenized with a stirrer at 200–300 rpm for half an hour. The obtained solutions were centrifuged for 5 min at 3600 rpm to remove air before casting. The solutions were poured into Petri dishes and dried at 50 °C for 16 h. The resulting dried films were used for extraction of the sol fraction using warm water (50 °C) under gentile magnetic stirring. The composition of the studied films is presented in Table 1.

6.3 Hydrogel Characterizations

The composite hydrogels were examined on a Jasco FT/IR6200 spectrometer (ABL& E-JASCO Romania) with Intron μ Infrared Microscope with ATR-1000-VZ objective. The spectra were the average of 50 scans recorded at a resolution of 4 cm^{-1} in a range from 4000 to 500 cm^{-1} with a TGS detector. For morphological observations, a scanning electron microscope FEI Quanta Inspect F scanning electron microscope (SEM) was used. All samples were gold coated prior to SEM examination. The thermal behavior of the hydrogels was tested using thermogravimetric analysis on a thermal analyzer (DTG-60-Shimadzu). The operating conditions were temperature range of 20–1000°C, with a heating rate of 10 °C/min, and air flow rate of 50 mL/min.

Swelling degree was determined as a function of time in deionized water. The average mass of the dried hydrogels was approximately 500 mg. The dried weighed samples were immersed in excess deionized water at ambient temperature and were weighed at different time intervals. The free water was removed using a paper towel to be sure that the net weight of each sample will be measured. The swelling degree (Q (g/g)) was calculated using Eq. 1.

$$Q = \frac{M_s - M_d}{M_d} \tag{1}$$

where M_s and M_d are the weight of the swollen and, respectively, of the dried film. Swelling kinetics was also measured using the same procedure, but the samples were weighed at predetermined time intervals.

Gel content was measured at room temperature. The pre-weighed hydrogel films were immersed in distilled water for 24 h, after which the samples were removed and dried at constant weight. Gel fraction (% w/w) was calculated using Eq. 2.

$$\text{Gel fraction} = \frac{W_2}{W_1} x100 \tag{2}$$

where W_1 is the sample weight before extraction and W_2 is the dried sample weight after extraction.

6.4 Results and Discussions

6.4.1 Gel Fraction

In Fig. 1 are presented the gel fractions for all the studied samples. As one can see, the values of the gel fractions are between 70% and 90%. The lowest gel fractions were obtained for the samples without XG (the films P1 and P2), and the highest values were obtained for a ratio CMC/XG 1:3 (w/w) (the films P5 and P6).

6.4.2 Swelling Properties of the Hydrogels

Swelling degree of the studied samples is presented in Fig. 2. One could observe large differences between the samples, in a good correlation with their composition. The samples which contain only CMC and citric acid (CA) in a ratio CMC/CA (4:1 w/w) have low swelling degrees. The BC presence enhances the swelling, but not very much. The swelling degree is 4.61 g/g for sample P2 in comparison with 3.73 g/g for sample P1. When XG is introduced in the hydrogel composition, the swelling degree is increasing with the increase of xanthan content. The highest swelling degree was obtained for the samples having a ratio between CMC/XG (1:6 w/w), CMC/CA (5:4 w/w), and XG/CA (7.5:1w/w). BC presence, even in a very low quantity if we report to its dry mass, has also influenced swelling degree by increasing it. Having in mind the aim of this work, to propose new biodegradable

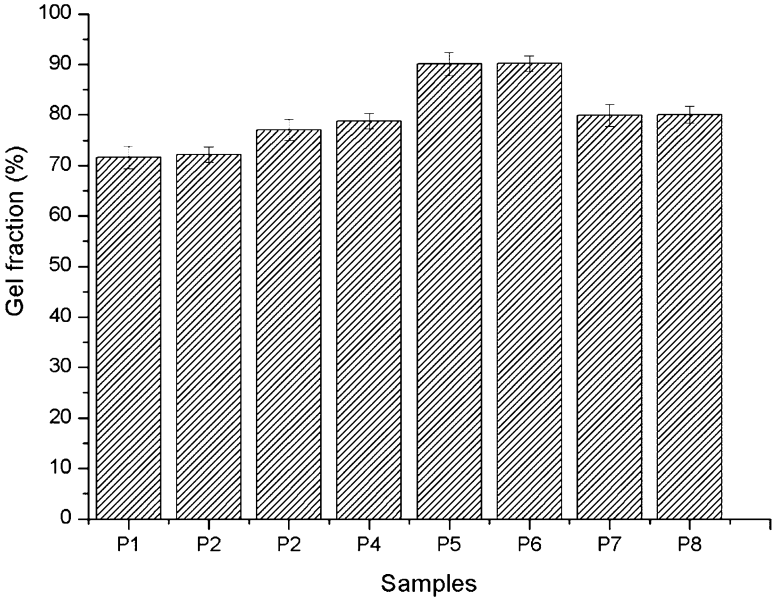

Fig. 1 Gel fractions for the studied samples

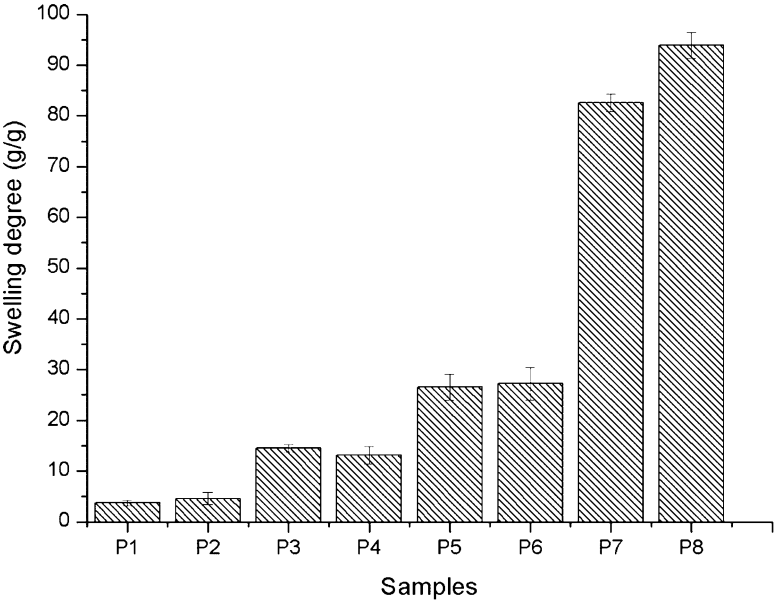

Fig. 2 Swelling degree for the studied samples

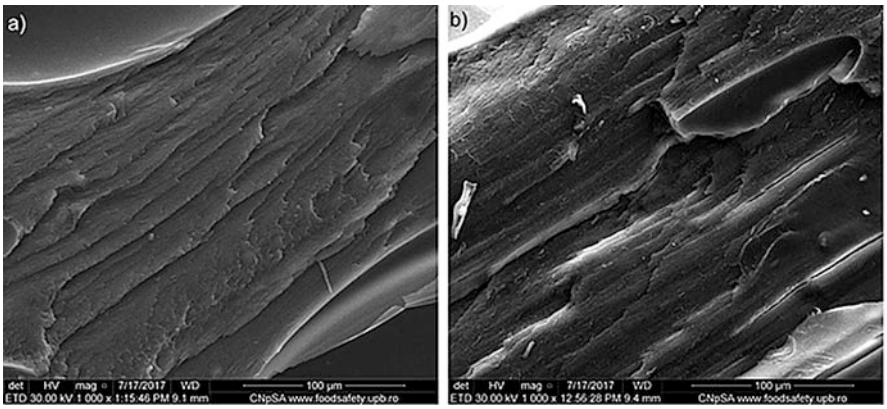

Fig. 3 SEM images of the samples (**a**) P7 and (**b**) P8

antimicrobial pads for food preservation, we have studied only the properties of the samples P7 and P8.

In Fig. 3 SEM images of the studied samples P7 and P8 are presented. A good compatibility between components could be observed. In Fig. 3b the presence of BC, even if it is in a low quantity, is observed as microfibrils dispersed in the hydrogel structure.

In Fig. 4 are presented FTIR spectra of the samples P7 and P8 which were tested to be used in food pad applications. The two spectra are practically identical, and the most of the absorption bands could be attributed to XG, which is an expected result, due to the hydrogel compositions (77% (P7) and 76% (P8) XG). The peak at 3331 cm^{-1} could be assigned to O–H stretching, and it is common for all the polysaccharides which are the components of the hydrogel (CMC for P7 and CMC and BC for P8). The same assumption could be made about the peaks at 1151 cm^{-1} (C–O–C asymmetric stretching vibration for glycosidic ring) and 1054 cm^{-1} (C–O–C pyranose ring skeletal vibrations) that are also common to all polysaccharides. The peaks between 1600–1640 and 1400–1450 cm^{-1} could be assigned to symmetric and asymmetric vibrations of ionized $–COO^{-}$ group. Bands between 1710 and 1730 cm^{-1} correspond to axial deformation of C=O ester, acid carboxylic, aldehydes, and ketones [139]. Unfortunately the presence of ester bonds could not be identified at 1730 cm^{-1} in the presence of citric acid, even if the mechanism of the crosslinking reaction between citric acid and the polysaccharides has been reported to take place by ester linkages formation [79].

The XRD patterns of the samples P7 and P8 are displayed in Fig. 5. The large and most intense band centered at about 20° was assigned to carboxymethylcellulose phase, which is the more crystalline in comparison with xanthan [140]. This band could also conceal the contribution of xanthan phase, which is the majority phase; however, its presence in crystalline form is slightly signalled through the flattened

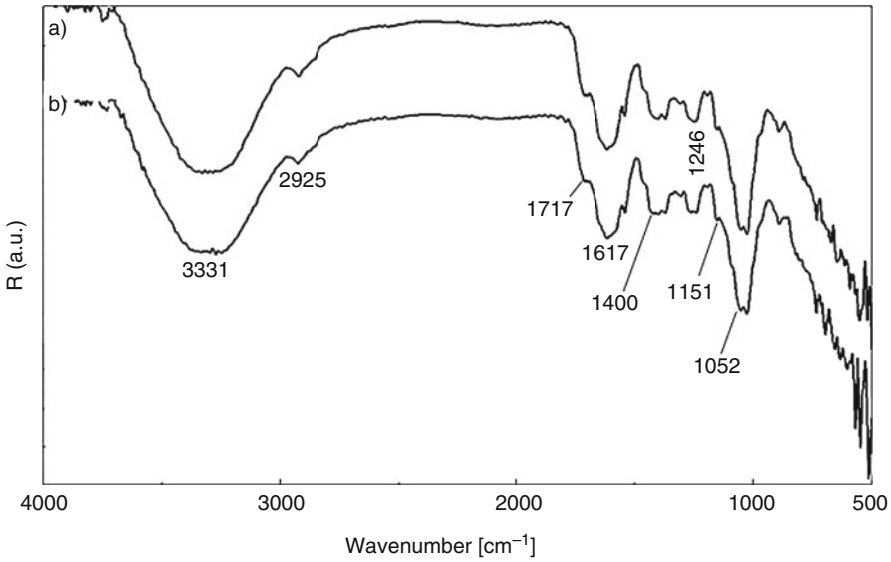

Fig. 4 FTIR spectra of the samples: (**a**) P7 and (**b**) P8

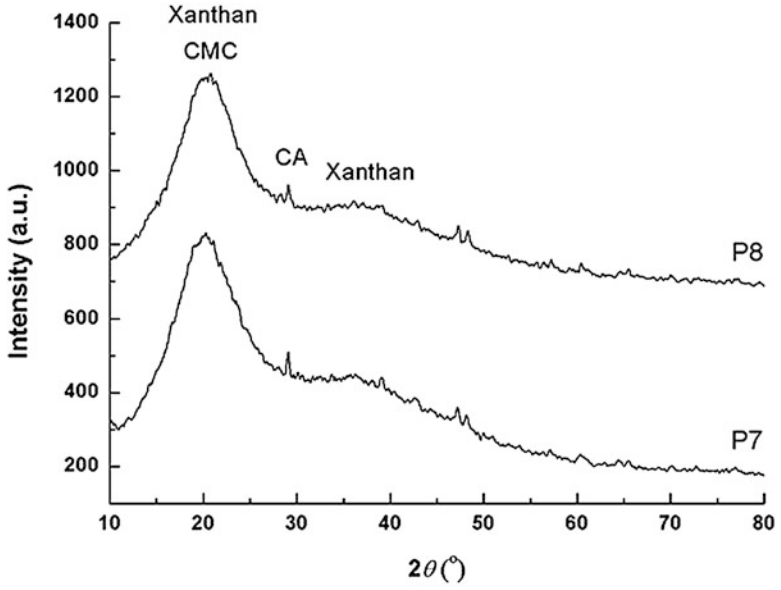

Fig. 5 X-ray diffraction patterns of the samples P7 and P8

and broad band places between 30° and 50° [80]. Xanthan is considered to be almost similar to that of a typical semicrystalline amorphous material [141]. The sharp peak centered at approximately 29° could be related to the use of citric acid for the preparation of the composites [142]. Unfortunately, the addition of bacterial

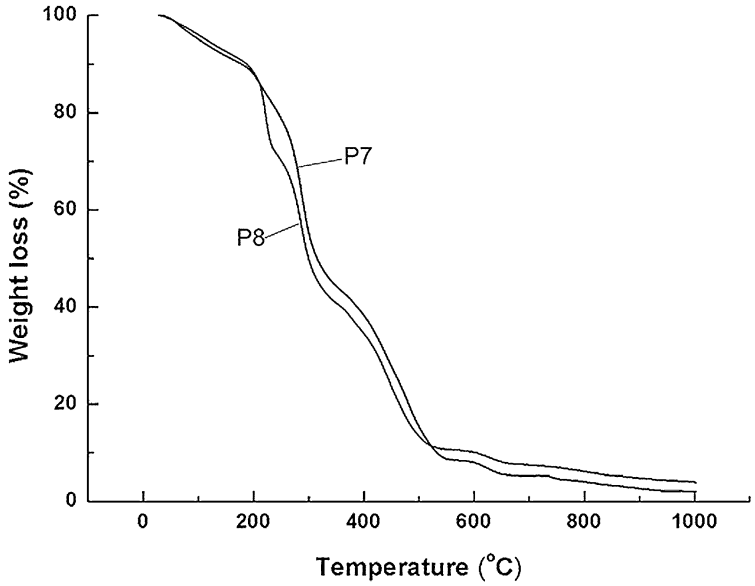

Fig. 6 TGA curves for the samples P7 and P8

cellulose in the sample P8 is not evidenced by this characterization technique due to the low content and pronounced contribution of carboxymethylcellulose.

6.4.3 Thermal Analysis

Figure 6 presents the corresponding TGA curves in a comparative approach. Generally, the thermal effects emerged for the investigated samples overlap on the entire temperature range, with some differences in terms of intensity. Three main weight loss steps can be identified on the derivative curves, associated with exothermic effects, showing the successive burning of the constituent polymers: citric acid at around 220 °C, xanthan at approximately 290 °C, and carboxymethylcellulose in the range 400–500 °C [143–145]. Considering the temperature of 560 °C, sample SP7 exhibits a weight loss of 91.42% while SP8 of 89.40%, a fact that indicates a slightly improved thermal behavior for the biocellulose containing material. Moreover, the weight loss occurred in the 170–240 °C temperature range is more pronounced in the case of P8, phenomenon that can be correlated with either the compositional changes or the existence of local inhomogeneity of the composite.

6.5 Adsorbent Pads with Antimicrobial Properties

In order to realize biodegradable adsorbent pads with antimicrobial properties, two problems must be solved. The first one is to cover the adsorbent material with an upper and lower layer. In some cases these layers are constituted by impermeable

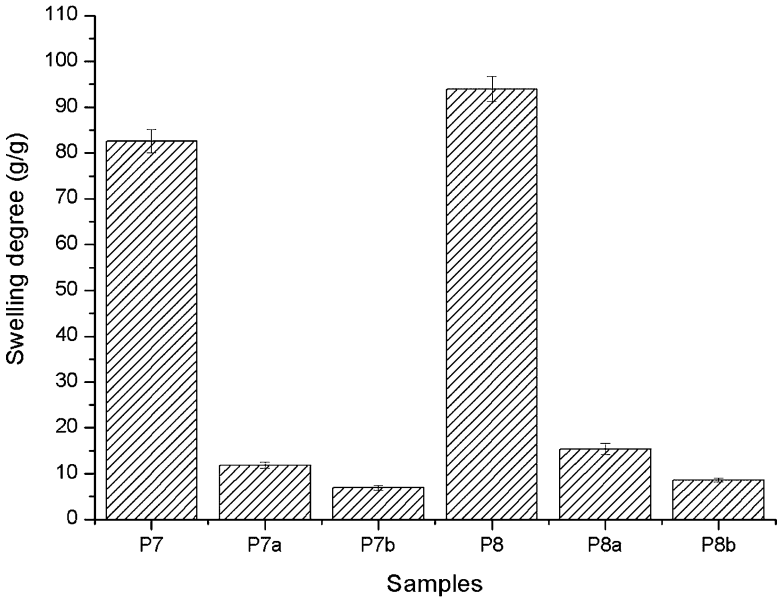

Fig. 7 Swelling degree for the uncovered (P7 and P8) and double-layer films (P7a, b and P8a, b)

thermoplastic material or by cellulosic materials [131]. More materials were tested as upper and lower layers for the sample P7 and P8. The first coating material was chosen based on previous experience as PVA/BC mixture [146].

6.5.1 Preparation of Double-Layer Composite Films

The above obtained composite films (P7 and P8) were coated with PVA/BC mixture. The monolayer films (P7 and P8) were dipped in the PVA/BC mixture and then carefully dried at 50 °C in order to obtain uniform coated layers. The coating layer was obtained by dissolving PVA in water under magnetic stirring at 90 °C for 4 h. In the PVA solution, were dispersed various amounts of wet ground BC fibrils corresponding to different ratios between the two biopolymers PVA/BC (5:0.2) and (10:0.2) (g/g expressed as dry mass). The covered films were noted P7a and P8a when the cover layer was composed of PVA/BC (5:0.2) g/g dry polymer and P7b and P8b when the cover layer was composed of PVA/BC (10:0.2) g/g dry polymer.

6.5.2 Swelling Properties of the Double-Layer Composite Films

In Fig. 7 are depicted the results obtained for the swelling degree of the covered samples in comparison with the uncovered ones. Even if a decrease of the swelling degree was expected, the measured decrease was a drastic one, and the new values were not acceptable for a food pads system. Under these conditions we have decided to test other materials which are biodegradable and which could act as cover layers without such decrease of swelling degree. As cover materials for the samples P7 and

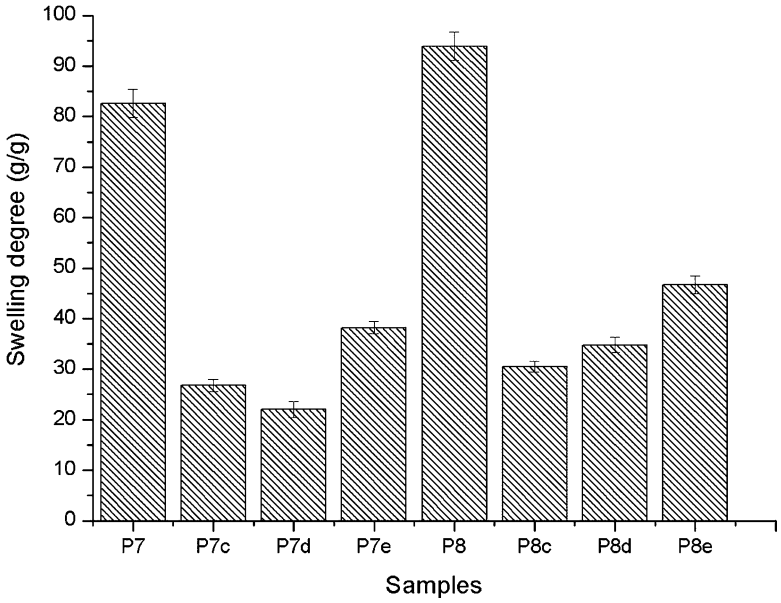

Fig. 8 Swelling degree for the uncovered (P7 and P8) and double-layer films covered with different materials

P8, were used gauze (P7c and P8c), flat cotton (P7d and P8d), and cellulosic composite paper with polyester (P7e and P8e).

In Fig. 8 are depicted the results obtained for the swelling degree of the new composite samples. In comparison with the uncovered samples, the swelling degree is also decreasing, but it is still maintaining at acceptable values for the samples P7e and P8e. So, we recommend as cover material the cellulosic composite paper with polyester.

6.5.3 Antimicrobial Agent Release

The samples P7 and P8 were also prepared adding to the initial compositions of two antimicrobial agents, a commercial one (potassium sorbate) and a natural one (thyme essential oil, ThEO). The release experiments of potassium sorbate were carried out cutting film disks with 2.5 cm diameter which were introduced in a backer containing 100 mL of distilled water. The diffusion medium was homogenized using a magnetic stirrer. Sample of solutions (0.1 mL) were removed at the predefined time intervals. The concentration of the potassium sorbate was measured by a UV/VIS spectrophotometer (Cintra 6-GBC Scientific-Australia) at 254 nm, using a previous performed standard curve.

In Fig. 9 are depicted the release profiles for the studied samples. One could observe that the quantity of sorbate released is higher for the sample P8.

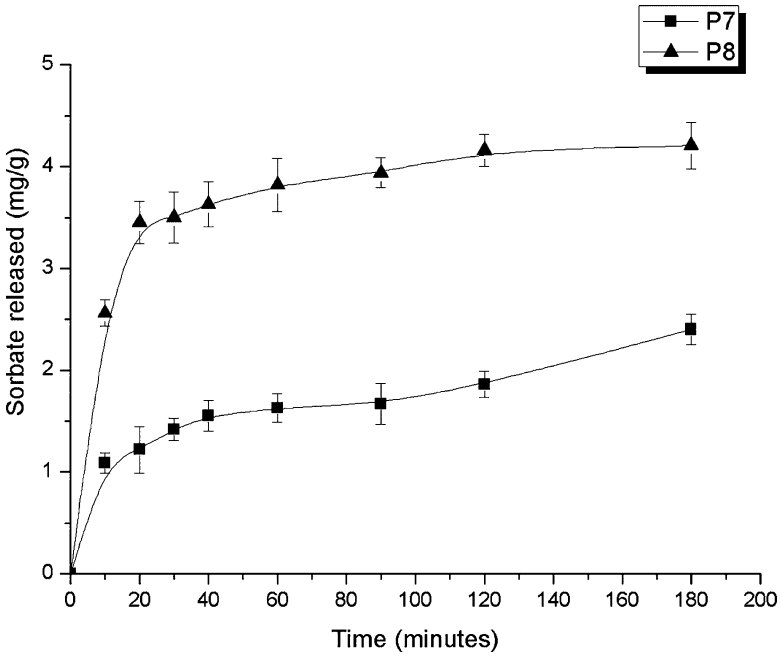

Fig. 9 In vitro cumulative release profiles of sodium sorbate: (■) sample P7 and (▲) sample P8

6.5.4 Antimicrobial Activity

As the antimicrobial activity of potassium sorbate is well documented, we have tested the antimicrobial activity of the superabsorbent film impregnated with thyme essential oil (ThEO). For the antimicrobial activity, were tested samples impregnated with ThEO in two ways: (1) a determined quantity of ThEO was poured in the film casting solution and dried at 50 °C for 16 h in an oven (code samples $P7_d$, $P8_d$), and (2) dried films without any microbial agent were impregnated on the surface with ThEO in concentration of 0.07, 0.14, and 0.21 μL/mm^2 (code samples $P7_f$, $P8_f$). Four microbial strains: *Escherichia coli*, *Bacillus subtilis*, *Candida utilis (Torula)*, and *Penicillium hirsutum*, were tested. The bacterial strains were cultivated on nutrient agar medium. For the yeast strain, were used YPD medium and for the mold strain the PDA medium. The method used to evidence the antimicrobial activity of superabsorbent films impregnated with ThEO was the disk diffusion method. The Petri dishes with the culture media specific to every strain were inoculated with 100 μL cellular suspension with the concentration of 1 in McFarland standards (equivalent of approximately $4 \cdot 10^6$ cfu/mL for bacterial strains and approximately $7 \cdot 10^5$ cfu/mL for fungi strains). On the surface of the inoculated media, were placed the disks of superabsorbent film impregnated with ThEO, with diameter of 6 mm. The samples were incubated at specific temperature of each strain: *E. coli* at 37 °C, *B. subtilis* and C. *utilis* at 30 °C, and *P. hirsutum* at 20 °C for 48 h, and after that were

kept at low temperature (4 °C). The results obtained for the samples impregnated in two different ways are presented in the images below. In Fig. 10 are presented the control samples for the superabsorbent films P7 and P8 studied, without antimicrobial ThEOs impregnations. The presence of the control samples didn't affect the microorganisms' growth.

Figures 11 and 12 show the fact that the samples impregnated on the surface with ThEO ($P7_f$, $P8_f$) completely inhibited the microorganisms' growth.

Superabsorbent films P7 and P8 impregnated with ThEO during casting solution preparation and then dried present a distinguishable inhibition zone, but also, the concentration of antimicrobial essential oil used exhibits the minimum inhibitory concentration (MIC), with purpose to ensure a long shelf life of the food product.

In Figs. 13 and 14, are presented the antimicrobial activities for the samples $P7_d$ and $P8_d$, against *Bacillus subtilis and Escherichia coli* (Fig. 13) and against *Candida*

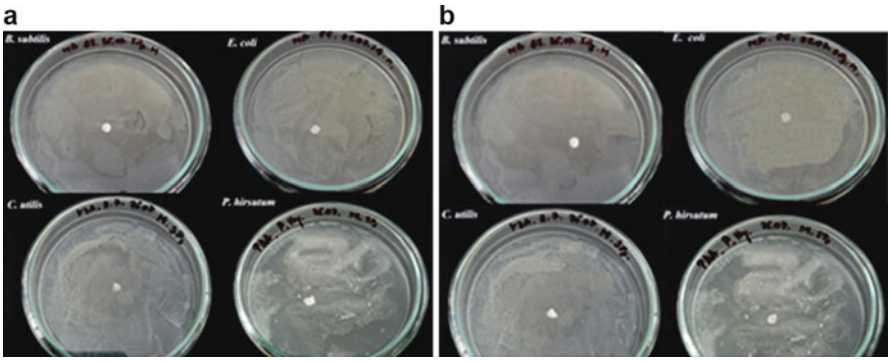

Fig. 10 The control samples against all microorganisms studied for P7 (**a**) and P8 (**b**) superabsorbent films

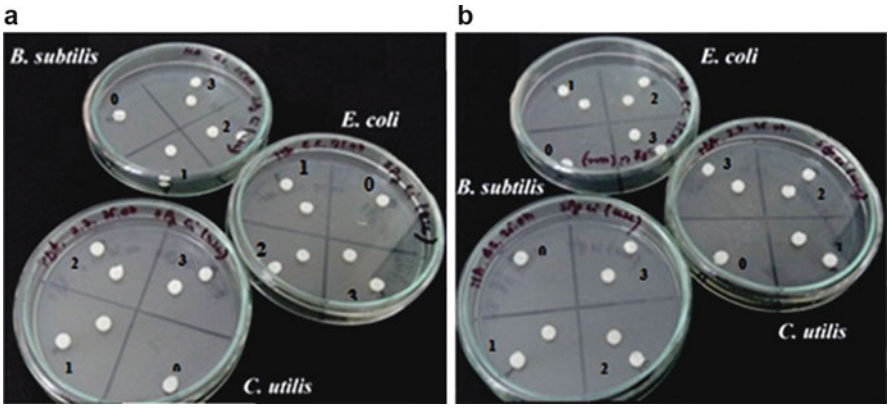

Fig. 11 Samples of $P7_f$ (**a**) and $P8_f$ (**b**) after 2 weeks of antimicrobial activity against three studied microorganisms. (0, ThEOs control sample; 1, 0.07 μL/mm^2 ThEOs; 2, 0.14 μL/mm^2 ThEOs; and 3, 0.21 μL/mm^2 ThEOs)

utilis (Torula) and *Penicillium hirsutum* (Fig. 14). The inhibition zones (IZ) were measured around the superabsorbent disks after 24 h. After 48 h from inoculation, the samples were stored in the refrigerator and kept for 2 weeks. The values of the inhibition zones after 2 weeks were also measured. In all studied cases, the film samples without ThEO didn't present antimicrobial activity.

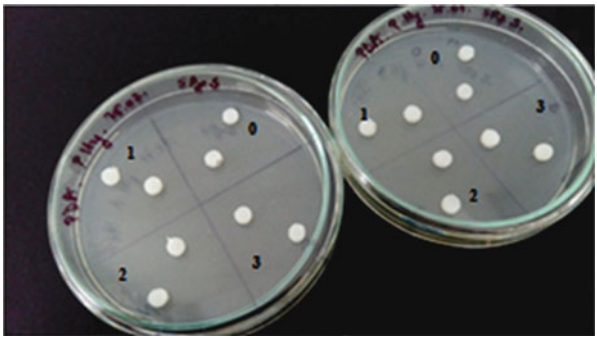

Fig. 12 Samples of $P7_f$ (**a**) and $P8_f$ (**b**) after 2 weeks of antimicrobial activity against *P. hirsutum.* (0, ThEOs control sample; 1, 0.07 μL/mm^2 ThEOs; 2, 0.14 μL/mm^2 ThEOs; and 3, 0.21 μL/mm^2 ThEOs)

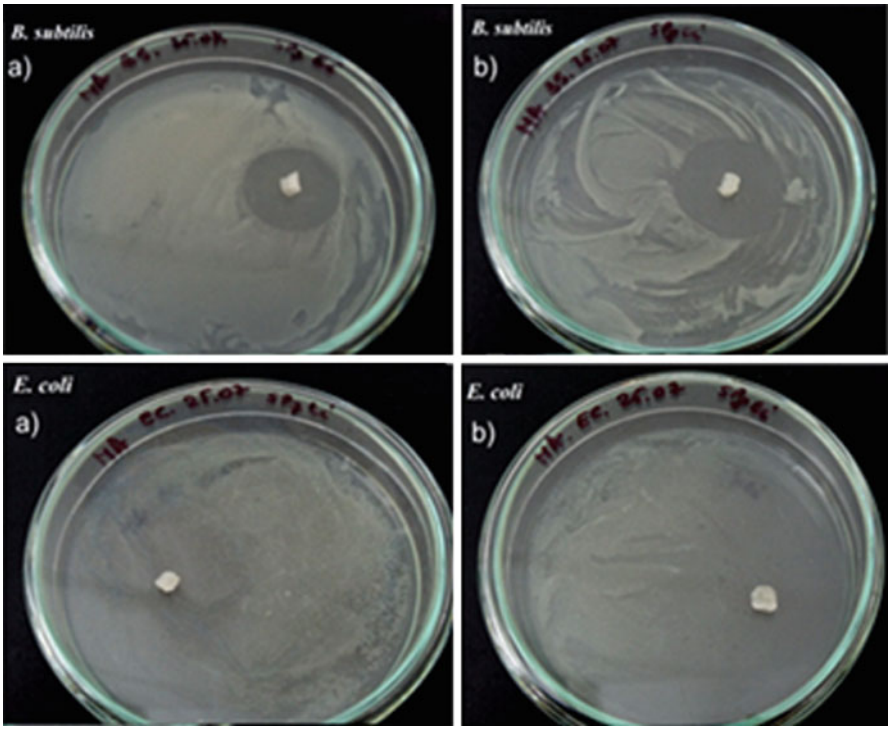

Fig. 13 Antimicrobial activity for samples (**a**) $P7_d$ and (**b**) $P8_d$ on *Bacillus subtilis and Escherichia coli*, after 2 weeks at 4 °C

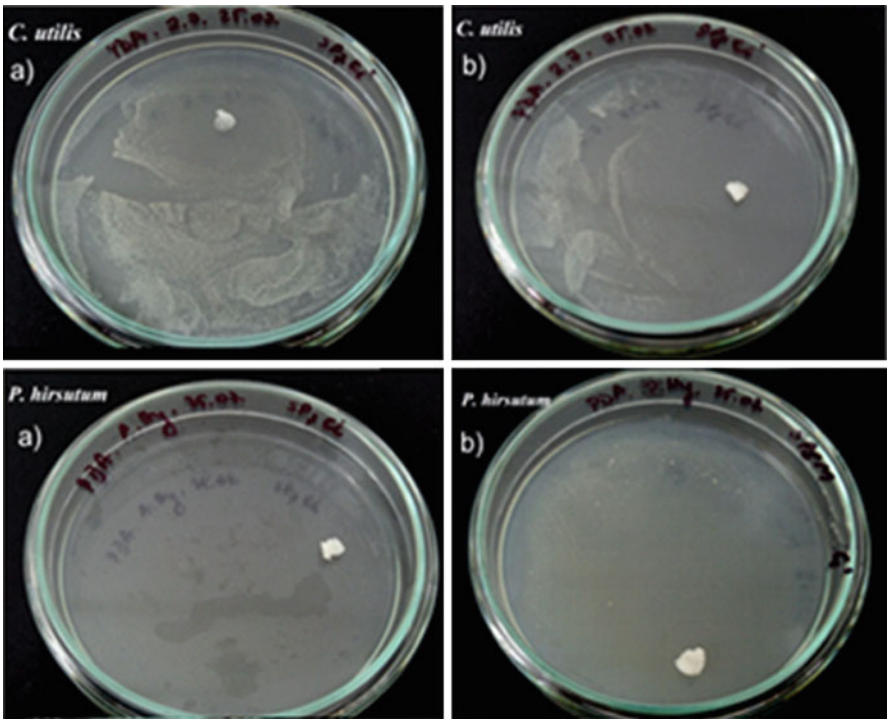

Fig. 14 Antimicrobial activity for samples (**a**) $P7_d$ and (**b**) $P8_d$ on *Candida utilis (Torula)* and *Penicillium hirsutum*, after 2 weeks at 4 °C

Table 2 The IZ recorded around the superabsorbent films containing ThEO, after 24 h of incubation at specific temperature of the selected microorganisms, using the disk diffusion method

Strain	Film code	IZ, mm
Escherichia coli	$P7_d$	10–15
	$P8_d$	>20
Bacillus subtilis	$P7_d$	10
	$P8_d$	15
Candida utilis	$P7_d$	5–8
	$P8_d$	>20
Penicillium hirsutum	$P7_d$	Negative results
	$P8_d$	>20

The results recorded after 24 h of incubation are presented in Table 2, and the results recorded after 2 weeks at 4 °C are presented in Table 3.

The results concerning the antimicrobial activity show that the concentration of thyme used for the two methods of impregnation was higher than MIC (estimated at 6 ppm for bacterial strains and yeast and 60 ppm for molds).

Table 3 The IZ recorded around the superabsorbent films containing ThEO, after 2 weeks of keeping plates at refrigerating temperature of 4 °C

Strain	Film code	IZ, mm
Escherichia coli	$P7_d$	10
	$P8_d$	>20
Bacillus subtilis	$P7_d$	8
	$P8_d$	10
Candida utilis	$P7_d$	6
	$P8_d$	>20
Penicillium hirsutum	$P7_d$	>20
	$P8_d$	>20

7 Conclusion

To extend the shelf life of food and maintain its nutritional properties and sensory characteristics is a challenge for food industry. But it is not the only goal as, at the same time, the packaging materials must be recyclable and biodegradable in order to minimize the environmental impact. In the present, non-biodegradable synthetic polymers are the most used as packaging materials having many useful properties. The first part of this chapter tries to answer to the two challenges of the food industry. Antimicrobial active packaging is proposed, among other solutions, to extend the shelf life of food, and a brief overview of the most encountered antimicrobial agents was made. The attention was focused especially on the application of natural antimicrobial compounds of different origins, emphasizing on essential oils and other plant extracts. To reduce environmental pollution with non-biodegradable plastics, the solution of the biopolymer composites is proposed, out of which cellulose and its derivatives are very good candidates. There are a series of difficulties which must be overcome because biopolymers do not have all the properties of synthetic polymers, and at the same time, they are more expensive. A lot of steps were already made in this direction, and the researchers have studied many possibilities to overcome these difficulties. The recent papers published in this field are a good proof in this respect. The overview was also oriented through food pads, antimicrobial moisture regulators being a solution for food spoilage. In the architecture of a food pad, the superabsorbent material plays a key role, and of this reason superabsorbents containing cellulose and its derivatives were briefly presented. In the second part of the chapter, experimental data are presented on obtaining and characterization of a new antimicrobial superabsorbent containing xanthan, carboxymethylcellulose, and bacterial cellulose.

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Cellulose-Based Hydrogel for Personal Hygiene Applications

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Contents

Abstract

Personal hygiene product is an inseparable part of urban society. It has given comfort, reliability, and flexibility to sick people, women, and children. The

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hygiene items containing superabsorbent polymer (hydrogels) for absorbing large amount of body fluids are the attractive inventions of modern science. The hydrogels swell and imbibe body fluids in the presence of hydrophilic functional groups in the polymeric backbone. Current trend of using acrylate-based superabsorbent in hygiene products is creating significant portion of urban garbage. This pile up is not only shrinking land sites but also harming a lot to the environment due to non-degradability of superabsorbent materials existing in the core of hygiene product. In spite of high water-holding capacity of petrochemical-based superabsorbent polymer, it has a hidden curse on nature of non-degradability and health risk. Cellulose is the most abundant biocompatible matter on this earth which basically originated from plants. It is also naturally occurring long chain polymer that plays a vital role in food cycle in animal kingdom. Besides this cellulose, its derivatives have large application in various fields. As cellulose and its etherified and esterified derivatives have attractive physicochemical and mechanical properties, hydrogels synthesized from cellulose and its derivative can be alternative to synthetic superabsorbent polymer. Cellulose-based hydrogels have found application in various fields like agriculture, biomedical, tissue engineering, wound dressing, pharmaceuticals, etc. Among various applications, some products are available in the market, and some are in research level. Due to fast swelling and other extraordinary properties (i.e., biocompatible and biodegradable), cellulosic materials (cellulose-originated hydrogels) can be applied in personal hygiene product so that superabsorbent from nonrenewable materials is partially or completely replaced. In this chapter, history of using superabsorbent in hygiene product, brief discussion on hydrogel synthesis, health and environment risk related to non-cellulosic absorbent materials, suitability of cellulose-based hydrogels over available acrylate hydrogels, and recommendation for development have been discussed.

Keywords
Cellulose · Hygiene products · Diaper · Hydrogel · Superabsorbent

1 Introduction

Cellulose is the most common and omnipresent biopolymer on earth, which is the essential ingredient of plants. Pure cellulose can be in different forms and varied in size, shape, and degree of crystallinity. The common forms are microcrystalline cellulose (MCC), powdered cellulose (PC), and low crystalline powdered cellulose (LCPC). All the forms have different mechanical, physical, and pharmaceutical properties. Cellulosic materials comprise pure cellulose and derivatives of cellulose. Among different derivatives, etherified and esterified derivatives are most useful for industrial purposes. Cellulose and its derivatives can easily be converted in to eco-friendly superabsorbent materials [1] that can be employed in numerous fields such as hygiene (disposable diapers and feminine

care products) [2, 3], agriculture (water retention and pesticide delivery) [4], biomedical materials (drug carriers, wound dressings, and tissue engineering scaffolds) [5–9], pollutant adsorbents (heavy metal ions, dyes, and pesticides) [10, 11], biosensors [12], etc.

From the definition, we can get information that hydrogels are hydrophilic polymer network which can swell on absorbing water without dissolving [13]. Hydrogels attract water due to polar functional groups on the skeletal of macromolecule and inhibit dissolving due to crosslinking. The amount of fluids taken up by the polymer network depends on the structure of the polymer network itself and on the environmental conditions, such as the temperature, pH, and ionic strength of the water solution in contact with the polymer [13, 14]. Hydrogels are of mainly two categories based on their natural or synthetic origin: biopolymer-based and synthetic. Hydrogels prepared at the early stage are non-biodegradable and originated from nonrenewable petroleum based. Among various biopolymers, cellulose is largely available in nature and shows hydrophilic nature and good mechanical properties because of enormous hydroxyl groups. The large number of hydrophilic functional groups in the structure gives possibility to cellulose as promising material for hydrogel preparation.

Hygiene products include disposable diapers, sanitary pads, and adult protective underwear for incontinence. Among the different products, disposable diaper is the largest consumer of superabsorbent polymer (SAP). In a disposable diaper, absorbent pad is used in addition to other construction materials. The absorbent pad is sandwiched between two sheets of fabric. The pad also consists of two layers in which the top layer is permeable and bottom layer is impermeable and absorbent materials remain between two layers. The absorbent materials are generally hydrophilic polymers such as sodium or potassium acrylate. The function of the polymeric materials inside the absorbent pad as the tiny sponges is to retain much water than their weight. At the same time with similar purposes, adult people use protective underwear during incontinence. Women also get comfort and protection in the sensitive period by the use of goods containing superabsorbent materials. Figure 1 shows construction and various parts of a diaper, and mechanism of attracting water molecules to hydrogels is shown. Though the materials have large capacity of water holding as well as body fluids, but due to uneco-friendliness, scientists are trying to replace the materials by cellulose-based hydrogels.

Any kind of hygiene product follows the common type of mechanism for water absorption. Most of the products are made up of a top layer containing spongy materials, and in most of the cases, it is fluff pulp. The material is capable of absorbing liquid very fast and makes room for further absorption by adsorbent material (i.e., hydrogel). Figure 1b shows the mechanism of absorption. As the adsorbent contains polar groups and water is also polar in nature, for this the water molecule is attracted by hydrogels and forms hydrogen bonds. Finally the hydrogel swells and holds the liquids excreted from the body.

The aim of the chapter is to make general idea about hydrogel and hygiene product to common reader and create source of thinking to the special reader

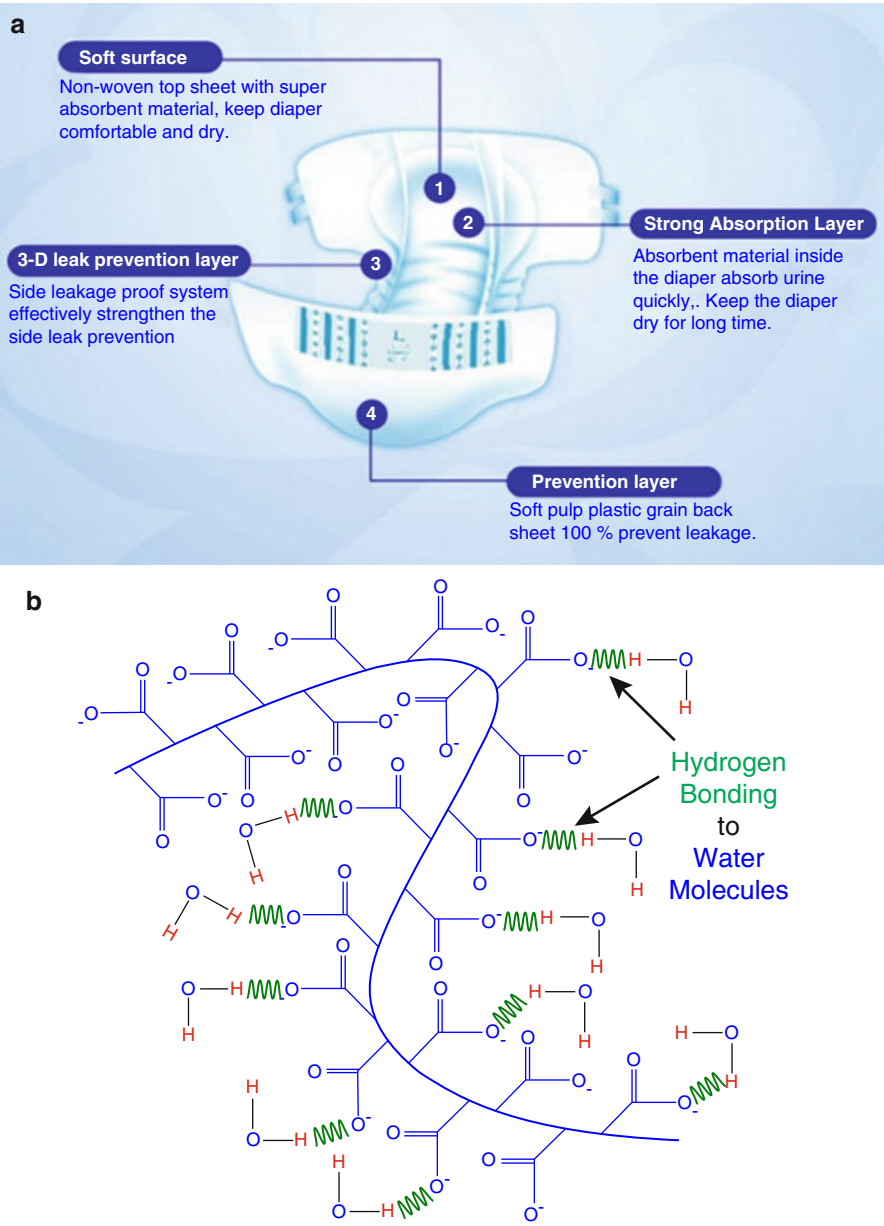

Fig. 1 (**a**) Various parts of a diaper and (**b**) way of combing water to the product

(researchers) to search ways of sustainability in personal care product manufacture as well as making the product biocompatible at the end of use, with the aid of cellulose and its derivatives.

2 Brief Description on Hygiene Products with Source and Polymeric Composition

The chapter demands some basic information about the types and construction of personal care products for general readers. It is mentioned earlier that disposable diapers, sanitary pads, and adult protective underwear for incontinence are common hygiene items and all the products consist of an absorbent core filled with hydrogels. In addition the products include the top layer of nonwoven or perforated film, a back sheet, and a fastening system. Again according to personal need, the hygiene product also varies in size, shape, and quality. The components are attached in such an organized way to gather the edges of the hygiene product into the proper shape so it fits snugly around a baby's legs and crotch or to elder persons. When the products fit properly (e.g., disposable diaper and rest of the hygiene products), they give comfort and retain body fluids which pass through the permeable top sheet and absorb into the pad.

Hygiene products differ from each other according to purposes and gender. For instance, feminine hygiene products are sanitary pads, tampons, panty shields that are common. Again diaper item includes baby disposable diaper, pant diaper, training pants for worker, and adult diaper for incontinence. Samples of hygiene products are shown in Fig. 2.

Diaper consists of mainly two parts: core and chassis. The core is mainly composed of polypropylene, cellulose, and a superabsorbent polymer, and chassis holds the core and attaches the diaper onto the baby and creates a proper fit around the legs. The top layer of a diaper is important as it remains in direct contact with baby's skin. The layer is designed such that the liquid passes rapidly toward the core. It is mainly made up of permeable polypropylene (PP) nonwoven. The next layer is made from fluff pulp and hydrogel, and the outer layer which prevents leakage of liquid is mainly made up of polyethylene (PE).

Among feminine hygiene products, sanitary pads and tampons are most frequently used. The common material as absorbent in these products is cellulose fluff, and modern trend is to use hydrogels for absorption which makes the product thinner and more reliable.

Elderly skin is sensitive to injury being thinner and has poor healing capabilities. In addition adult incontinence is not always accompanied by fecal incontinence as in baby diaper. People with different ages and different complexities are the user of the product. Adult diapers also consist of similar materials in construction as baby diaper but the absorption capacity is higher compared to baby diaper.

Hydrogel is an interesting field of research, and before studying its application elaborately, it is logical to get idea about classification of the materials. Many authors tried to classify hydrogels through various perspectives or viewpoints taking into consideration of many factors. In this section, only classification of hydrogels based on source from which the product is synthesized has been discussed.

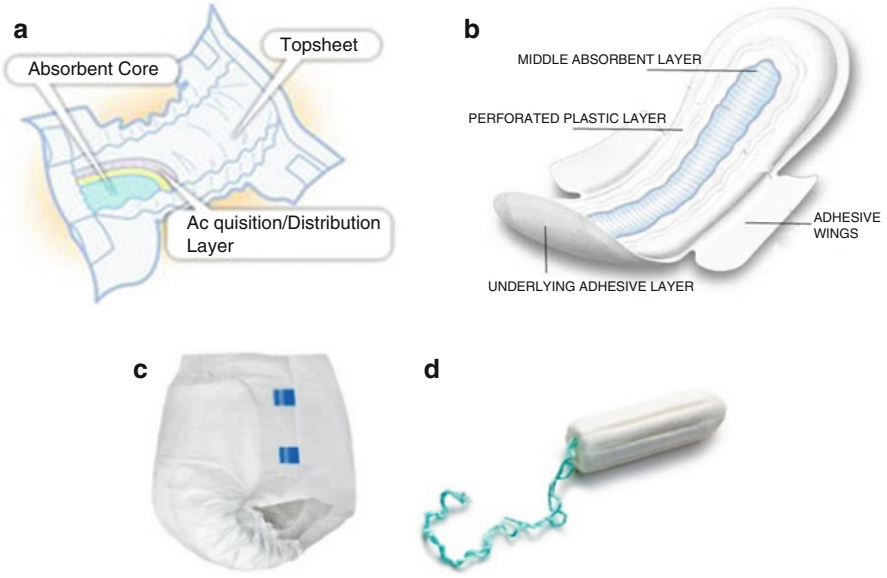

Fig. 2 (**a**) Disposable diaper, (**b**) sanitary pad, (**c**) adult protective underwear, and (**d**) tampon

2.1 Hydrogels Based on Source and Polymeric Composition

Hydrogels are generally originated from two main sources, and they are synthetic (petrochemical based) and natural [15]. Hydrogels synthesized from natural sources can also be divided into two main groups, i.e., polysaccharide-based hydrogels and others are polypeptide (proteins) based. In real practice, natural-based hydrogels also contain synthetic parts. Generally hydrogels are prepared through addition of some synthetic monomers onto the natural substrates, e.g., graft copolymerization of vinyl monomers on polysaccharides.

On the basis of starting materials, hydrogels can also be classified as natural polymer hydrogels, synthetic polymer hydrogels, and combination of the natural and synthetic. Again methods of preparation of hydrogels change to the types of product. Using a number of monomers for the synthesis of hydrogels gives hydrogels with different properties. Classes of hydrogels based on polymeric composition are described below:

2.1.1 Hydrogels from Homopolymer

Homopolymer means that the product is derived from the same monomeric unit. When the hydrogel is derived from single monomer, it is homopolymeric hydrogel, and it is the fundamental structural unit from which the whole chain grows. Depending on the type of monomer and polymer technique, the growing chain may have cross-linked skeletal structure [16].

2.1.2 Hydrogels of Copolymers

Copolymer results from the combination of two or more different types of monomers. Copolymer-containing hydrogels are formed by two or more different monomer species among them at least one hydrophilic component, arranged in a random, block, or alternating arrangement along the chain of the polymer network [17].

2.1.3 Hydrogels of Interpenetrating Polymeric Network (IPN)

This is an important class of hydrogels, which is prepared from two independent cross-linked synthetic and/or natural polymer components, arranged in a network form. In semi-IPN hydrogel, there are two components among which one is of cross-linked polymer and the other is a non-cross-linked polymer [18].

3 Methods of Synthesis of Cellulose-Based Hydrogels

Hydrogels are polymeric substances, and they are generally prepared from one of the two common pathways: (a) polymerization reaction among hydrophilic monomers and (b) renovation or reactivation of existing polymeric substance (natural or synthetic).

There are mainly two original sources from where hydrogels are synthesized, i.e., synthetic or petrochemical based and natural. Natural sources can also be classified into two groups, i.e., polysaccharide-based (mainly cellulosic) and polypeptide-based hydrogels. The synthetic sources are hydrophobic in nature but chemically stronger. After polymerization, hydrogels gain hydrophilic character. The strength of nature is responsible for slow degradation rate as well as provides the durability of the product. Scientists are searching to bring balance through optimal design between the two opposite qualities to make product successful to the consumer [19]. Recently considering the environmental issue, scientists are designing hydrogels from natural sources and also meeting the expected demands of durability and degradability. As the sources contain suitable functional groups or have been functionalized with radically polymerizable groups, they can be converted to eco-friendly hydrogels [20].

In a fundamental concept, as hydrogels are cross-linked polymeric substances, so any technique which is used to produce cross-linked structure can also be suitable for hydrogel preparation. Among various techniques, copolymerization/crosslinking of monomers through free radical mechanism is commonly used to prepare hydrogels in the presence of multifunctional crosslinkers. Some commonly followed steps for hydrogel preparation are:

1. Formation of polymer chains via chemical reaction.
2. Assistance of ionizing radiation to generate main-chain free radicals propagate reaction to enlarge chain and recombine as cross-link junctions.
3. Instead of chemical, physical interactions such as entanglements, electrostatics, and crystallite formation are used to form polymeric chain.

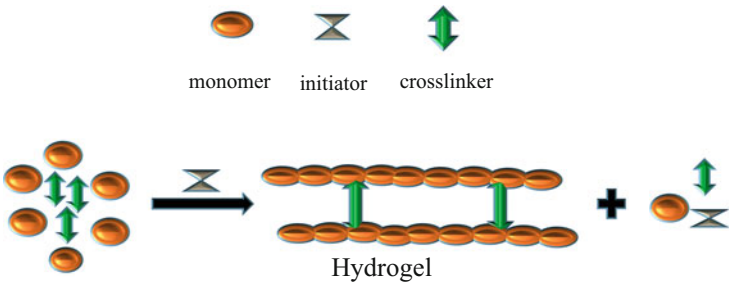

Fig. 3 Schematic diagram of hydrogel preparation

The most frequently used polymerization techniques are bulk, solution, and suspension polymerization, any one of which can be used to form hydrogels. The compulsory components of the whole process of hydrogel formation are monomers, initiators, and crosslinking agents. Moreover diluents like water or other aqueous solution play an important role to control the heat of polymerization. At the end of the reaction, the final product requires washing to remove impurities left from the preparation process like non-reacted monomer, initiators, crosslinkers, and unwanted products produced via side reactions (Fig. 3). Polar or hydrophilic monomers are generally used to manufacture hydrogels. Hydrogels can be obtained through various polymerization techniques with different size and shape and including desired physical properties for a given application.

Each of the polymerization technique has some positive achievement for the finished product as well as darken contribution. Bulk polymerization is the simplest technique which contributes high rate and degree of polymerization. Hydrogels from the bulk polymerization is homogeneous, glassy, and transparent but very hard. The glassy matrix swells in water to become soft and flexible.

An important class of polymerization technique for hydrogel synthesis is suspension polymerization. The product obtained by this technique in the form of powder or microspheres (beads) for this grinding is not required. The process is advantageous than bulk polymerization due to used solvent system where water-in-oil (W/O) system was used instead of common oil-in-water (O/W). As the process is thermodynamically unstable, there requires continuous stirring and addition of a low hydrophilic–lipophilic-balance (HLB) suspending agent [21].

In some application, graft copolymerization is a useful tool to improve hydrogel quality. Grafting onto a strong support is an old concept but helpful in property enhancement of weak structure. The technique involves formation of free radicals of support onto which monomers will combine through covalent bonding [22].

Besides discussing different polymerization techniques, one of the main objectives is to describe briefly the factors affecting synthesis of cellulose-based hydrogels. It is possible to obtain cellulose-based hydrogels from cellulose and its

derivatives. The inherent fact of cellulose-based hydrogels has also been disclosed in earlier part of the chapter that this type of hydrogels contains a cellulosic part and another synthetic part. Synthesis technique consists of physical or chemical stabilization of aqueous solution of cellulosics (cellulose and its derivatives). For this the hydrogels containing both cellulose and synthetic part are termed as composite hydrogels which also gain specific properties [23]. Cellulose-based hydrogels stabilized physically are synthesized from aqueous solution of methyl and/or hydroxypropylmethyl cellulose [24], and they are thermoreversible in nature. In this case, gel formation mechanism includes addition of hydrophobic macromolecules containing methoxy groups. At low temperature, hydration of polymer chains takes place in solution which propagates entanglement of chains. Further increase in temperature makes it possible to dehydrate from entangled chain which also gears up hydrophobic association of chains, and finally polymeric network of hydrogels is formed.

The degree of substitution of cellulose ethers as well as addition of salts controls the solgel temperature of the system. Higher degree of substitution of cellulose derivative results to more hydrophobic character of polymer chain which is necessary for hydrogel network formation. Salt concentration also gives similar result. It was found that hydrogel for biomedical application requires specific properties which can be obtained from hydrogels with specific formulation. It was also reported that by adjusting degree of substitution and salt concentration and keeping temperature at 37 °C, obtained hydrogel is suitable for biomedical application [25, 26].

It is found that physically cross-linked (i.e., high-energy radiation) hydrogels are stiff and stable and have flow properties; the same result of crosslinking can be obtained in case of using suitable chemical agent that gives stable cellulose-based networks. In both cases, degree of crosslinking (the number of crosslinking sites per unit volume of the polymer network) is an important factor which affects the diffusive, mechanical, and degradation properties of the hydrogel. The degree of crosslinking can be controlled in a number of ways, and chemical modification of cellulose backbone is the most popular and common of them. Few published articles report that some chemically modified cellulose derivatives are used for hydrogel preparation and showed potentiality in biomedical application [27].

Another remarkable factor which is essential to think before designing a hydrogel is the biocompatibility of crosslinking agents. The most widely practiced crosslinkers for cellulose are epichlorohydrin, aldehydes and aldehyde-based reagents, urea derivatives, carbodiimides, and multifunctional carboxylic acids. Be aware about toxicity of them like aldehydes. Recently it has been reported that cellulose-based hydrogels cross-linked with citric acid are biocompatible as well as show good swelling.

Due to consideration of environmental and safety aspect, scientists show more interest to radiation crosslinking of polymers, based on gamma radiation or electron beams. Though it is not risk free, but it has more potentiality in biomedical application with controlled dose of radiation [28, 29].

4 History and Present Scenario of Hydrogels Used for Personal Hygiene Product

In 1938 water-absorbent polymer found its success, and that time it was prepared by thermal polymerization of acrylic acid and divinylbenzene in aqueous medium [30]. Later in 1950, Otto Wichterle synthesized first-generation hydrogel from poly (hydroxyethyl methacrylate) (PHEMA) and used it for soft contact lenses preparation. Though the preparation was synthetic, but it was a revolution in ophthalmology [31]. Since the 1970s, diaper technology has been flourishing, and about 1000 patents have been issued for last 25 years on the construction and design of diapers and reached at present condition. Japan started their first commercial production of hydrogel in 1978 for use in feminine napkins, and later in 1980, Germany and France started using it in baby diaper [32]. Japan started manufacturing disposable diaper in 1983 with 4–5 g SAP hydrogel in every single piece of diaper. Within very short time, other countries in Asia, the USA, and Europe also started manufacturing diaper with hydrogels. Introduction of SAP hydrogels in personal hygiene product (i.e., diaper and napkin) was a turning point of the concept of using the items for self-protection and comfort. All the synthesized products were synthetic in nature and lack of degradability; scientists started to prepare hydrogels from cellulosic sources which had good absorption and biocompatible property.

From an online market survey report [33] in the Asia-Pacific region, China is the biggest market, and the USA is the largest end user and producer of SAP in the North American region. According to that report in 2014, Asia-Pacific was estimated as the largest market for SAP with the largest share of the overall SAP market in terms of value. For that year, North America and Europe together accounted for more than 40% of the global SAP market in terms of value. The amount of SAP was estimated at 2.07 million tons in 2014, and the amount will reach to 3.1 million tons in 2023; the worth of the product will be 11 billion USD.

Another international research organization [34] gives an idea about the worldwide consumption of hydrogels. The demand for hydrogel has increased across a number of applications and has pushed manufacturers to increase their manufacturing capacities. Research activities in the medical and pharmaceutical industries have risen the demand of hydrogel all over the world. High birth rate, reducing mortality rates, rising per capita income, and consciousness about health are also responsible to drive upward hydrogel demand. According to the TMR report, North America led the global hydrogel market with an overall share of 37.2% (in the Fig. 4 below) in terms of value, with a CAGR value of 6.3% in 2016. They also gave a projection about the global market of hydrogel that the demand expanding at a CAGR of 6.3% from 2017 to 2025, worth from US$10,084.9 mn in 2016 to US$17,487.6 mn by the end of 2024.

Again from an online presentation given by a diaper consultant (Carlos Richer, https://www.linkedin.com/in/carlosricher), the number of adult people at the age of 70 will be 563 million in the year 2023, and one in every three requires protection for incontinence. The same report gives the projection that in 2025 the world number of

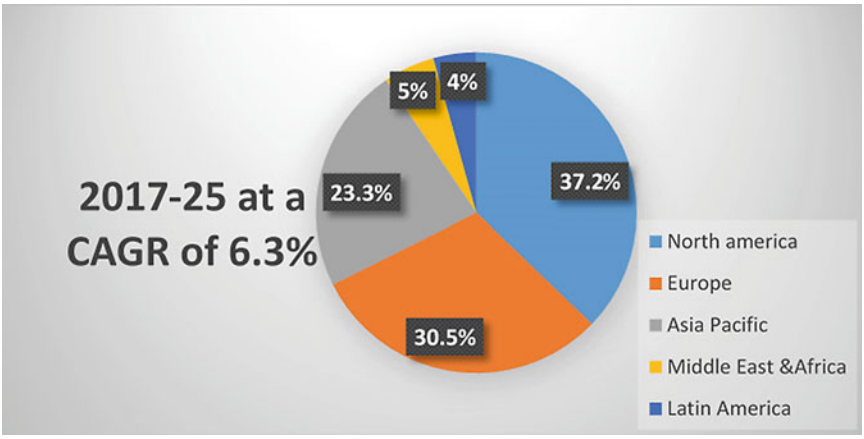

Fig. 4 Hydrogel market share by region (TMR)

babies will be 328 million and this will require a large number of disposable diapers [35].

The first commercially available American disposable napkins for menstrual protection were Lister's Towels created by Johnson & Johnson in 1896 [36]. From then various types of product have been developed, but at present most of the manufacturers are preparing product with petroleum-based absorbent in core of the product. Feminine hygiene products ensure women to lead a healthy and sound life. Currently rising awareness about hygiene among women has changed a massive chunk in the demand of personal hygiene product across different countries. Feminine hygiene products include not only items of special time but also other items like wash/gels, wipes, and moisturizers. All the products find application in protection, skin care, revitalization, and moisturizing. Easy availability of the products is also responsible for global demand of feminine hygiene product. A report published in *USA TODAY* newspaper with the reference of Global Industry Analysts that current market of $5.9 billion of feminine hygiene products in the USA and $35.4 billion on worldwide. That amount would be expected to top $40 billion around the world in the next 3 years [37]. The conclusive form of that report was represented by bar diagram given in Fig. 5.

Finally the successive application of hydrogels in personal hygiene product as absorbent materials is discussed in the table below for better understanding and to get clear idea about the use of hydrogels (Table 1).

5 Application of Cellulose-Based Hydrogels

Cellulose and its derivatives are low priced, renewable, and biocompatible and can be applied to manufacture hydrogels where biodegradability is prime important. In this section, application of cellulose-based hydrogels in personal hygiene care and

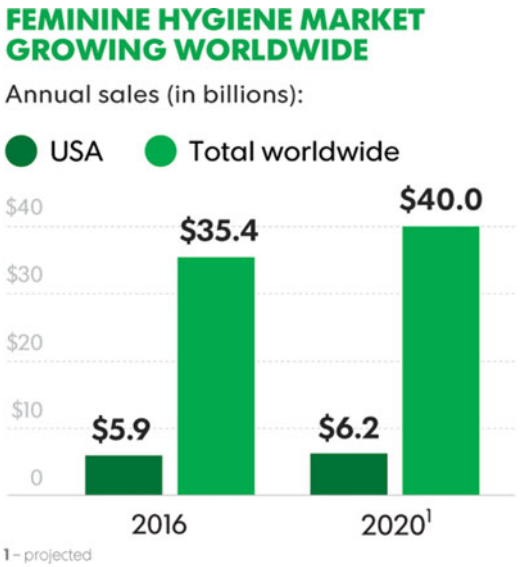

Fig. 5 Feminine hygiene product market growing analysis by Global Industry Analysts [37]

Table 1 Summary of events in modern hygiene product history

Event	Corresponding year
First water-absorbent polymer	1938
Synthesized first-generation hydrogel from poly (hydroxyethyl methacrylate, PHEMA) and used for soft contact lenses	1950
Japan started their first commercial production of hydrogel for use in feminine napkins	1978
Germany and France started using hydrogels in baby diaper	1980
The journey of innovation (high and rapid absorption capacity, biocompatible, cost-effective, etc.)	Till today

other traditional use of hydrogels as water absorbents to more innovative biomedical applications have been discussed.

5.1 Personal Hygiene Care

Superabsorbent hydrogels are the common ingredients for personal hygiene care products (diaper, sanitary napkins, and adults underwear for incontinence). These products keep individuals dry, safe, and out of embarrassing situation at definite time period. Some articles have been published concerning about the advantages of using superabsorbent hydrogels for personal care products especially in diapers [38]. For the recent couple of years, the business of parents has grown much which makes them dependent on diaper for their babies. Modern SAP-based leak-proof

disposable diapers not only keep them dry and prevent skin diseases but also control the risk of fecal contamination in day-care play areas and other places. Now it is a proven truth that SAP-based diapers play a vital role in reducing the risk of illness of children and building a healthy society [39]. The use of SAP materials in personal hygiene product was not an old fashion; it only started in 1982 by Unicharm in Japan which is used first in sanitary napkins and later in baby diaper. It made diaper thinner with less weight and better performance in leakage handling [40]. A statistic revealed the fact that a child till the age of 30 months using disposable diaper creates about 1092 m^3 of garbage per year which requires removal and almost 1500 m^3 of diapers as garbage requires cleaning from a city of 1 million population. As it was a tedious job, many attempts have been taken to make reuse of the items like disposable diapers, napkins, hospital bedsheets, sanitary towels, and other similar products [41]. There are some common materials in these hygiene products which are biodegradable and others are not. Generally the cellulosic part is recyclable and biodegradable, and the objectives of recycling is to separate the ingredients for further use. Since the task was complex, it made scientists to think alternatively, and making the ingredients biocompatible is only solution. As cellulose-based SAPs are biodegradable, it can be a good alternative solution of the problem. It has been reported that hydrogels synthesized from sodium carboxymethylcellulose (NaCMC) and hydroxyethyl cellulose (HEC) cross-linked with divinyl sulfone (DVS) show good water retention capacity under centrifugal loads [3]. Concerning with environmental impact, cellulose-based hydrogels are very much suitable for hygiene product to make them eco-friendly and decomposable. In this regard, using nontoxic crosslinking agents [42] will be more fruitful attempt, and introduction of radiation technique will make the process more acceptable [2].

5.2 Water Conservation Aid in Agriculture

Cellulose-based hydrogels have other interesting and attractive applications. One of the promising applications of hydrogels is in agriculture. Sources of underground water are shrinking, and scientists are trying to consume rainwater by holding sprayed water for a long time for cultivation. In arid and desert regions of the world, where scarcity of water resources is an unbearable problem, the xerogel (i.e., dry hydrogel), in form of powder or granules, can be a helpful tool in agriculture. At the time of cultivation, water or nutrients mixed water are sprayed; the water is absorbed by the hydrogel, which then releases to the soil as needed, thus keeping the soil humid over long periods of time. Many research articles have been published mentioning application of hydrogels in agriculture; among them Sannino and coworkers recently developed cellulose-based superabsorbent hydrogels which are totally biodegradable and biocompatible and able to absorb up to 1 l of water per gram of dry material, without releasing it under compression [43].

5.3 Biomedical Application

Due to the property of biodegradability shown by the cellulosics, hydrogels synthesized from them also become biodegradable. In addition they have many similarity with body tissue, for this many researchers found potentiality to apply hydrogels from cellulose and its derivatives in biomedical application. As cellulose-based hydrogels swell in the presence of water and degrade, it can be applied as devices for the removal of excess water from the body and in the treatment of some pathological conditions, such as renal failure and diuretic-resistant edemas [44].

5.4 Pharmaceuticals

Cellulose and its derivatives have wide application in pharmaceutical sectors. Few are available in commercial scale, and the rest are in research level. Among the derivatives, etherified derivatives are more widely used than the others. The commonly used ether derivatives are methyl cellulose (MC), ethyl cellulose (EC), hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), hydroxypropylmethyl cellulose (HPMC), carboxymethyl cellulose (CMC), and sodium carboxymethyl cellulose (NaCMC). They are used in pharmaceutical as bio- and mucoadhesive in drug delivery system, pharmaceutical coatings, extended release solid dosage forms, osmotic drug delivery system, compressibility enhancer, gelling agents, thickening and stabilizing agents, fillers and binders, disintegrating agents, and taste-masking agents [45, 46]. The simplified mechanism of drug delivery system in body fluid is shown in Fig. 6.

5.5 As Supporting Materials in Treatment

The World Health Organization gives information about modern health problem like obesity and overweight; one in every three adult population is overweight, and one

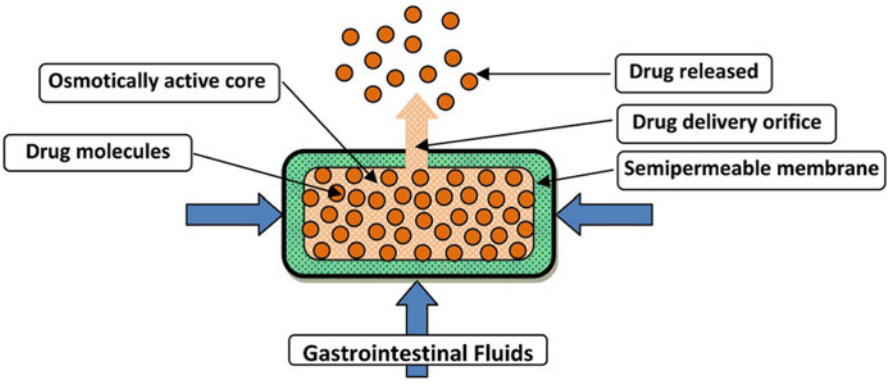

Fig. 6 Schematic diagram of an EOP (elementary osmotic pumps) system [47]

in every ten is obese. Another alarming information is that more than 20 million children under age 5 are overweight. These two reasons are responsible for several chronic diseases, such as type 2 diabetes, cardiovascular disease, sleep apnea, hypertension, stroke, and certain forms of cancer. Doctors generally suggest supervised diet or dietary supplements combined with adequate physical exercise for the treatment of obese and overweight. Hydrogels can act as dietary supplements. It is reported that novel cellulose-based hydrogels, obtained by crosslinking aqueous mixtures of NaCMC and HEC, have been shown to be appealing for the production of dietary bulking agents [48].

5.6 Wound Dressing

One of the established applications of cellulosed-based hydrogels is wound dressing. Different types of dressing products are in the market, and in some cases, product with antimicrobial agents is also in the market to ensure sound cure. Few hydrogel dressings have been patented so far and are available in the market, based on synthetic or natural polymers or a combination of them. Due to high purity, good air permeability, and good water retention capacity, bacterial cellulose (BC) has been widely investigated for wound healing, and the product is also in the market.

Cellulose-based hydrogels have also found less but not least in other applications like cosmetics and perfume industry, scaffolds for regenerative medicine, and environmental protection [49, 10].

At a glance, one can get an overall idea of vast sectors of application of hydrogels from Fig. 7.

6 Health Risk of Hygiene Product and Impact on Nature

The common health problem from which most of the babies suffer is diaper rash (Fig. 8a). It occurs on babies' skin in different rates, at least once every couple of months it is common but some seem about all the time. Diaper rash is a type of irritation of skin boosted up by enzymes in baby's poop, diaper friction, and wetness as well as yeast in some cases. It is reported that sometimes baby diapers contain traces of dioxins and the World Health Organization recommends dioxins are "persistent environmental pollutants" that can be responsible for many health problems including developmental delays, damaged immunity, hormone interference, and certain cancers. Another detrimental effect to health is that disposable diapers release volatile organic compounds (VOCs) such as ethyl benzene, toluene, and xylene, and according to the EPA (The United States Environmental Protection Agency), some VOCs are carcinogens.

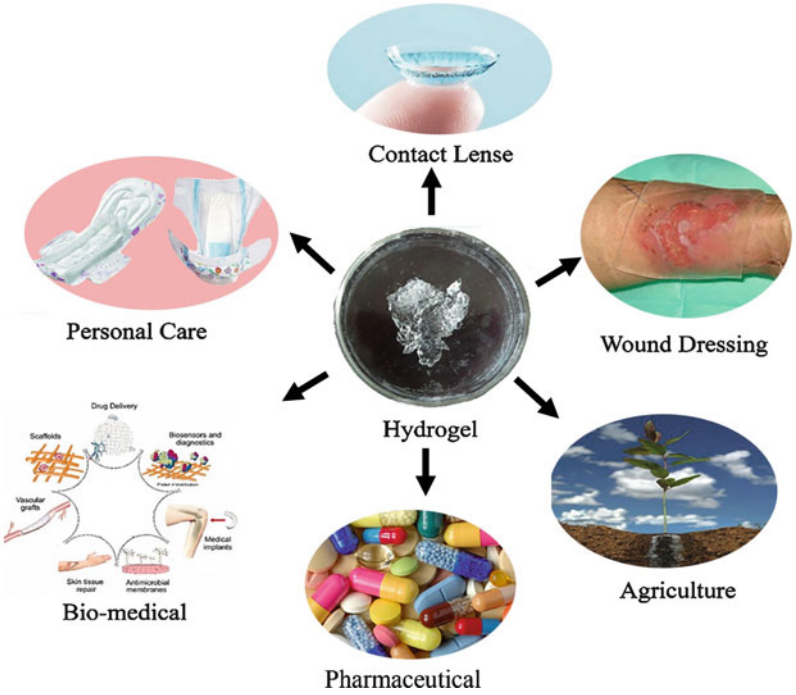

Fig. 7 An overview of application of cellulose-based hydrogels [Ref]

Many health disorders are found to take place in relation to the use of napkins, and the common incidents are toxic shock syndrome, skin irritants, staph infections, and urinary tract infection and may be related to other health problems.

Most of the absorbent center in disposable diapers and napkin is made of sodium polyacrylate (SAP), which is a petrochemical-originated synthetic chemical. In addition many hygiene products use dyes, and most of the dyes are chemically derived from either petroleum or coal tars. Coal tar is a carcinogenic liquid or semiliquid that is obtained from bituminous coal and often contains a number of toxins, including benzene, xylene, naphthalene, phenol, and creosol. Again in some cases, the dyes are resistant to biodegradation. Therefore these chemicals can be harmful even after they leave the hands of the user, as they become water pollutants and are highly toxic to aquatic life.

SAP was responsible for the cases of toxic shock syndrome in both diapers and napkins and skin irritation, urinary tract infection, and other health problems.

Moreover handling of such huge number of solid garbage created from diapers and other hygiene product is very much difficult (Fig. 8b). It is found from a statistical data that there are about 50,000 diaper user among 1 million population in the USA and this requires necessity to remove 150 m^3 of diapers from a city [41]. The addition of millions of tons of untreated waste of diaper and napkins added to landfills each year is a national problem.

Fig. 8 (**a**) Diaper rash in a child body and (**b**) dumping site of garbage (hygiene products and others) in the USA [50, 51]

7 Suitability of Cellulosic to Overcome the Hindrance

Cellulose is the polymer of glucose, renewable, abundant in nature, and found more or less in all parts of the world. Though it is mainly originated from plants, but some bacteria are able to synthesize cellulose [52]. Both the celluloses are insoluble in water and other solvents due to high crystallinity in the structure. To make the cellulose dissolve or transform into working condition, it requires modification. As cellulose contains numerous hydroxyl groups, these sites can be modified through

chemical reaction. Etherification and esterification are two processes to bring change in hydroxyl groups of cellulose. Cellulose derivatives are called cellulosics which are found eco-friendly as they are decomposed by several bacteria and fungi present in air, water, and soil [53]. It is also investigated that modification lowers crystallinity which results rapid degradation and enhances solubility.

Biocompatibility of cellulose and its derivatives prompted it to apply in various fields especially in personal hygiene product as well as biomedical application. As human or animal tissue cannot synthesize cellulase (enzyme), cellulose cannot be absorbed by them. The thing is that cellulose will degrade slowly and the matter was observed by many scientists, and Martson and his coresearchers are pioneer of them [54–56].

Most of the etherified derivatives of cellulose are water soluble, and during the reaction, the hydroxyl groups are most vulnerable sites where alkyl units can be attached. Many attempts have been made by scientists to synthesize hydrogels from cellulose derivatives like methylcellulose (MC), hydroxypropyl methylcellulose (HPMC), ethyl cellulose (EC), hydroxyethyl cellulose (HEC), and sodium carboxymethylcellulose (NaCMC), and many articles are also published, and finally they are used in food, pharmaceutical, and cosmetic industries, due to their high solubility, biodegradability, and biocompatibility, non-toxicity, and competitive low cost than the synthetic one.

In addition sodium carboxymethylcellulose (NaCMC) is polyelectrolyte which can show smart behavior (responsive to pH and ionic concentration); these effects impose positive effects to the hydrogels containing CMC during swelling and show suitability for smart application [57].

8 Conclusion

Modern age is the age of science, and the society is accompanied with many conscious, sincere people and well-wisher to mankind. Though concept of hygiene product is primitive, but research has brought newness of the items. The authors tried to give introduction of the products to general readers as well as some clues where scientists have opportunity to keep contribution. Actually science is always giving restless effort to make the world better for living. If personal hygiene product becomes flawless, the newborn, women, and elders will lead a sound life. In this respect, cellulose is the eligible candidate to solve the problem.

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Part V

Other Bio-Based Hydrogels and Their Applications

Synthetic Hydrogels and Their Impact on Health and Environment

46

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Contents

Abstract

Hydrogels have been discovered nearly 60 years ago and due to their permeability to water systems, they have become very important materials for use in comparison to other polymers. Hydrogels are materials first rationally designed for use in human medicine, and they find important usage in various areas, for example, in products for personal care, pharmaceutical, agriculture, and environmental protection. Especially interesting is the class of stimuli-sensitive hydrogels, due to

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their properties to respond to changes in pH, temperature, and ionic strength of the surrounding medium, whereby changes exist in the network structure, for example, swelling properties. Hydrogels have significant applications: in diagnosis, as substrates or implants in tissue engineering, as drug delivery carriers, and in cosmetics. Water pollution by heavy metals and dyes is a major environmental problem because of toxicity to the living world, bioaccumulation, and bio-non-degradability. Adsorption of heavy metals, radioactive elements, and dyes using the hydrogels is an effective way for their removal. The mechanism of heavy metals and dye ions removal using hydrogels could be explained by the physical adsorption, hydrogen bonding, complexation, and/or chelation and ion exchange. The pollutants adsorption process using hydrogels has some important advantages compared to conventional techniques: high adsorption capacity for removal of pollutants from aqueous solutions, binding ability, and reusability (regeneration). Hydrogels have applications in some systems for the controlled and sustained release of pesticides and fertilizers, so reducing the contamination of the soil and surface water by these agrochemicals.

Keywords
Hydrogel · Synthesis · Controlled/modified release · Drug carrier · Adsorption · Pollutants

1 Introduction

From the first hydrogels invention till nowadays, researchers have been defining hydrogels in many different ways [1–4]. According to Grant & Hackh's Chemical Dictionary, hydrogel is defined as a solid, cross-linked three-dimensional network which swells in water, and the hydrophilic macromolecules contain 20–95% of water [5]. Hydrogels can be described as hydrophilic polymers which do not dissolve, but can swell in surrounding fluid [6]. The most common definition is that hydrogel is a water-swollen, cross-linked polymeric network obtained by a simple reaction of one or more monomers. Hydrogels are adsorptive materials composed of hydrophilic polymers linked through chemical or physical cross-linking in such manner that they can absorb and retain large volumes of water within their three-dimensional network without dissolution [7]. The hydrogel water absorption ability originates from hydrophilic functional groups, attached to the polymeric backbone, while their resistance to dissolution is a result of cross-links between chain networks. The network component of a hydrogel is usually a polymer network, while a polymer network without water is xerogel. After contact between water and xerogel, water molecules infiltrate in space between the polymer chains, the polymer network volume increases, whereby hydrogel is swelling. The cross-linked hydrogel immersed in a fluid reached equilibrium swelling state with its medium, which is a result of only two opposing forces, the thermodynamic force of mixing and retractive force of the polymer chains [4].

The characteristic hydrogels property, their behavior to adapt structural changes in response to various physical or chemical changes, makes them intelligent candidates for controlled/modified release of pharmaceutically active substances. Because of large water content, hydrogels possess a degree of flexibility very similar to the natural tissue. This is usually achieved by a low cross-linking degree, similar to the case of conventional elastomers. Hydrogel matrices comprise a wide range of natural and synthetic polymers with physical or chemical cross-links. During the last few decades, synthetic hydrogels were gradually replacing natural hydrogels, because of their high capacity of water absorption, better mechanical properties, and long service life. Synthetic hydrogels have well-defined structures which may be designed for better yield, flexible degradability, and functionality [7].

Scientists have growing interest to remove toxic pollutants from aqueous solutions because of their negative effects on the environment. Heavy metals are toxic at very low concentrations. They are also characterized by a tendency of bioaccumulation and non-biodegradability. Dyes are toxic and carcinogenic substances, which by low concentrations in water cause a change in color, causing blocking of the sun's rays and disrupting the process of photosynthesis. Radioactive elements in the human body can cause damage to cells, liver, kidney, and pancreas, which leads to cancer. Therefore, several different techniques for removing these pollutants have been developed [8–13].

Traditional methods for the removal of pollutants (filtration, ultrafiltration, electrolysis, reverse osmosis, and ion exchange) exhibit certain limitations, such as low efficiency and high cost of the process. Another disadvantage is the production of sludge, which must be adequately treated in the later stages. Among alternative methods of purifying contaminated water, adsorption was distinguished due to cost-effectiveness and flexibility [14].

Synthetic hydrogels have structural flexibility, thermal and mechanical stability, and functional groups (carboxyl, amides, etc.) which allow binding of organic and inorganic pollutants [8, 15]. Facility of the incorporation of different chelating groups makes these hydrogels adequate for environmental application [16].

Conventional application of agrochemicals, pesticides, and fertilizers can lead to contamination of the soil; therefore it is necessary to reduce the active ingredients concentration without any impact on the efficiency. Suitable systems for controlled release of agrochemicals are hydrogels which are three-dimensional matrices for absorption and release of these substances depending on external conditions [17, 18]. Hydrogels with many desirable properties have huge practical applications, particularly in arid regions for improving water retention in sandy soils and the water supply to plants grown on them [19].

The aim of this chapter is to show the wide variety of synthetic hydrogel applications, at first, in the human health with their use in pharmacy and in cosmetics, including aspect of their safety and potential toxicity. Secondly, this chapter provides recent trends in synthetic hydrogels usage for removal of pollutants, dyes, heavy metals, and radioactive elements and for controlled release of agrochemicals, including their impact on the environment.

2 Hydrogels Classification and Development

The hydrogels may be classified in many different ways [1–4]. The polymer chains of a hydrogel are cross-linked and based on the nature of cross-linking there are two general classes, physically and chemically cross-linked hydrogels. Polymer chains of physically cross-linked hydrogel are held together by electrostatic forces, hydrogen bonds, hydrophobic interactions, or chain entanglements. Polymer chains of chemically cross-linked hydrogels are connected by permanent covalent bonds.

According to the origin of monomer, hydrogels can be natural (based on natural polymers, e.g., starch, cellulose, proteins, dextran, chitosan, alginate, fibrin, collagen, gelatin, hyaluronic acid), synthetic (obtained by polymerization reactions of vinyl monomers, e.g., *N*-isopropylacrylamide, 2-hydroxypropyl methacrylate, vinyl acetate, acrylic acid, methacrylic acid, ethylene oxide, or other reactants), and a combination of natural and synthetic types.

Hydrogels were divided into neutral and ionic hydrogels, in relation to side group's polarity. Ionic hydrogels may be anionic, cationic, and amphiphilic. Based on the swelling behavior to variations in the external medium, there are conventional hydrogels and stimuli-responsive hydrogels (which show significant changes in volume, shape, and mechanical properties due to changes in the external environment). According to a type of stimuli, there are several types of stimuli-responsive hydrogels: pH-responsive, temperature-responsive, double pH- and thermo-responsive, biomolecule-responsive, pressure-responsive, and hydrogels responsive to ionic strength, to electrical impulses, to ultrasound, to magnetic fields, and to light [4].

Based on pore size, hydrogels were divided into superporous (pore size >100 μm), macroporous (pores size 0.1–1 μm), microporous (pores size 0.1–0.01 μm), and non-porous hydrogels (pores size 0.001–0.01 μm). Based on polymer network nature, there are homopolymer, or copolymer hydrogels, interpenetrated, or semi-interpenetrated networks.

Related to behavior in a living organism, hydrogels can be biodegradable and non-biodegradable. Based on behavior in a living organism, hydrogels can be non-toxic and toxic.

A historical overview of the developments in hydrogel research over the last 50 years, starting with the relatively simple, chemically cross-linked networks of the 1960s and concluding with today's "smart" hydrogels, can be presented in following way [20]:

- The first-generation hydrogels described were hydrogels prepared by polymerization of water-soluble monomers (poly(hydroxyalkyl methacrylate)s), hydrogels based on cross-linking of water-soluble synthetic polymers poly(vinyl alcohol) (PVA) and poly(ethylene glycol) (PEG), and hydrogels based on cellulose.
- The second-generation hydrogels comprise of temperature-sensitive hydrogels (based on PEG-polyester block copolymers, poly(*N*-isopropylacrylamide) (PNIPAM), or other thermoresponsive systems) and in situ forming hydrogels based on other stimuli.

– The third-generation hydrogels comprise of stereocomplexed hydrogels, e.g., poly(ethylene glycol)-poly(lactic acid) interaction [21], and hydrogels cross-linked by other physical interactions (e.g., cyclodextrins). This progress leads to growth of the "smart hydrogels," with a wide spectrum of suitable properties and trigger stimuli.

Stimuli-responsive hydrogels are described as smart or intelligent gel when its sol–gel transition occurs at conditions, that can be induced in a living body, to deliver active substances at various times or sites in the surrounding medium, according to stimulus that is applied [22, 23]. The smart polymers originated from ability of hydrogels to imitate the non-linear response of deoxyribonucleic acid (DNA) and proteins [24].

Superabsorbent polymers (SAPs) are special class of weak cross-linked hydrogels which can absorb and retain large amounts of water, up to thousand times greater than their weight in dry state (1000 $g/g_{xerogel}$) [25, 26]. They have super-high absorbing capacity in a wide pH-range with possibility for re-use after easy regeneration [27]. The presence of strong repulsive forces between functional groups with the same electric charge in the hydrogels structure is the fundamental prerequisite for the utilization of superabsorbent.

2.1 Synthetic Hydrogels Synthesis

Hydrogels based on synthetic polymers include poly(hydroxyalkyl methacrylates), poly(acrylamide), PAM, poly(ethylene oxide), poly(*N*-vinyl-2-pyrrolidone), and PVA. Synthetic hydrogels are chemically stronger compared to natural hydrogels. Their mechanical strength results in slow degradation rate, but it provides good durability [28]. The hydrogels may be synthesized in a conventional manner, or by various other approaches by copolymerization, free radical polymerization, genetic engineering, irradiation, photo-polymerization, reversible addition-fragmentation chain transfer (RAFT), atom transfer radical polymerization (ATRP), and nitroxide-mediated polymerization (NMP) techniques. The novel methods of cross-linking used in the hydrogel synthesis, the water transport mechanism through the hydrogels, and release mechanism of the solute from the hydrogels are investigated in numerous scientific researches [20]. The cross-linking degree can be correlated to basically every characteristic of a hydrogel. By controlling the cross-linking degree, it is possible to tune the material property and optimize it for many different applications starting from the original polymer/monomer. The probable way of monomers bonding during polymerization is a formation of mixed structures with random, statistical, unsystematic arrangement [23, 29].

Some of the hydrogels can be prepared without the initiator by polycondensation (or polyaddition) cross-linking reactions. The water-soluble polymers have functional group (generally OH, COOH, and NH_2) which can be used for the hydrogels synthesis. Networking between polymer chains can be carried out by reaction

between functional groups with complementary reactivity, such as amine/carboxylic acid reactions, isocyanate/OH-NH_2, or the Schiff base forming.

In situ chemically cross-linkable hydrogels can be polymerized through covalent cross-linking between polymers with complementary functional groups that occur under physiological conditions with minimal toxicity [20]. Hydrogel formation can be catalyzed using enzymes, i.e., peroxidase, transglutaminase, tyrosinase, and transferase [30–32]. These hydrogels are injectable, biodegradable, and applicable to tissue engineering, gene therapy, and medical and dental adhesives. They can mimic extracellular matrices, but they are limited by the stability of used enzymes.

Radical polymerization is a usual method for obtaining smart hydrogels. Monomer, initiator, and cross-linker, as reactants, diluted in adequate solution (i.e., water) are polymerized after initiation using temperature, UV-, γ-, or electron beam radiation, or by chemically initiation. Initiation of polymerization is most often carried out chemically with free radicals, azo compounds or peroxides, persulfates, or redox initiators for polymerization in water. After synthesis, purification of synthesized hydrogels is needed to eliminate impurities, unwanted side reaction products, oligomers, and residual reactants. PNIPAM known as a typical negative thermosensitive hydrogel exhibits a lower critical solution temperature (LCST) in water. By temperatures below LCST, hydrogen bonding between the polymer and water molecules is responsible for the hydrogel swelling. When the temperature is raised above LCST, a hydrophobic interaction dominates, leading to hydrogel contraction. Various publications have described in detail synthetic methods and applications of hydrogels. For example, thermosensitive homopolymer PNIPAM [33] and copolymer poly(*N*-isopropylacrylamide/2-hydroxypropyl methacrylate) [23, 29, 34], have been synthesized in acetone as a solvent via free radical polymerization. Similarly, pH-sensitive poly(hydroxyethyl methacrylate/methacrylic acid) [35] and poly(acrylic acid/methacrylic acid), P(AA/MAA), [36] hydrogels were synthesized by radical mechanism in water.

The photopolymerization reaction is initiated by decomposition of a photoinitiator, resulting in the formation of radicals and subsequent network formation. Bioerodible hydrogels based on poly(ethylene glycol)/poly(α-hydroxy acid) diacrylate macromers have been first synthesized by a photopolymerization method in 1993 [37]. Also, the network formation between (meth)acrylate functionalized polymers can occur in the presence of UV or visible light [38, 39]. Photopolymerized hydrogels are being investigated for a number of tissue engineering applications, because of the ability to form these materials in situ in a minimally invasive manner, such as by injection. The pH-sensitive poly(methacrylic acid/poly(ethylene glycol) methacrylate), P(MAA/EGMA), hydrogel microparticles were synthesized via dispersion photopolymerization. There was a drastic change in the swelling ratio of synthesized microparticles at a pH of around 5 [40].

Polymerization of PVA aqueous solution by irradiation using gamma rays from cobalt-60 was carried out firstly in 1958 [41]. By sufficient dose of radiation, the polymer molecules in the solution interlinked with each other and formed an insoluble gel. The irradiation technique was used by a number of research groups to prepare PEG hydrogels [42, 43].

The preparation of hydrogels by radiation treatment of aqueous solutions of hydrophilic monomers or polymers has some advantages over conventional techniques. It does not require initiators, cross-linkers and can be used practically with any vinyl monomer and both polymerization and cross-linking reactions can be initiated at ambient or sub-ambient temperatures.

Double-network hydrogels responding to both pH and temperature are generally prepared from copolymers with pH-responsive moieties (i.e., *N,N′*-diethylaminopropyl methacrylamide or acrylic acid, AA) and temperature-responsive moieties (i.e., *N*-isopropylacrylamide, NIPAM) with combination of physical, covalent, or ionic bonds. The first hydrogels responding to more than one trigger were prepared by combining pH and temperature-induced gelation in 1992 for the release of amylase [44]. The dual-gelling hydrogels from thermosensitive vinyl functionalized PNIPAM and thiol have been synthesized by Michael-type addition reaction [45]. Poly(*N*-isopropylacrylamide-*co*-hydroxyethyl methacrylate) macromers with either alkyne or azide functionalities were in situ stabilized by "click" chemistry [46]. The resulted hydrogels had a macroporous structure as well as a fast shrinking rate swelling and compressive mechanical properties, because of the spatial hindrance of polymeric chains. Dual-gelling thermally and chemically cross-linkable hydrogels based on PNIPAM and dimethyl-γ-butyrolactone acrylate were successfully developed and physico-chemically characterized [47]. The temperature- and pH-sensitive copolymer hydrogels based on itaconic acid (IA) and NIPAM, which was reacted with acylated hemicellulose and PVA, were synthesized by Liu and colleagues [25]. LCST of these hemicellulose-containing hydrogels varied from 34 °C to 44 °C depending on NIPAM and IA mass ratios.

Hydrogels with high absorbing capacity, so-called superapsorbing hydrogels (SAPs), may be obtained by cross-linking copolymerization method using, e.g., AA with various synthetic monomers (i.e., vinyl monomers – NIPAM, sulfopropyl methacrylate potassium salt, and potassium acrylate) as well as with natural polymers (i.e., carboxymethyl cellulose and gelatinized corn starch) [19, 48–50]. Polyacrylate is the primary material used in the industry of superabsorbent hydrogels. The synthesis of hydrogels with fast swelling kinetics and superabsorbent properties called "superporous" was obtained with introduced interconnected pores to the polymer network [51]. These hydrogels have the pore size in the xerogel state about hundreds of micrometers. The superabsorbent hydrogels sensitive to temperature and pH changes, poly(*N*-isopropylacrylamide/acrylic acid), P(NIPAM/AA), were obtained via free radical polymerization method in presence of appropriate cross-linker agents, initiators, and solvents [52, 53]. Hydrogels after lyophilization swell faster and achieve higher absorption capacity of the surrounding fluid in comparison to non-lyophilized samples. Temperature and pH of the medium have impact on hydrogel swelling, so P(NIPAM/AA) hydrogels reached equilibrium swelling degree $\alpha_e = 259.8$ at pH = 6.8 at 25 °C. They can be classified as superabsorbent polymers because they have equilibrium swelling degree higher than 100. Superporous hydrogels are applied in production of disposable diapers, pharmaceutical dosage forms, packages, water-swelling rubbers, fire-extinguishing gels, and soil conditioning and water storage in the soil as well [54]. Chitosan/poly

(vinyl alcohol) interpenetrating polymer network type superporous hydrogels were prepared by using gas foaming method, with glyoxal as the cross-linker. These superporous hydrogels were highly pH sensitive and showed reversible swelling and de-swelling behavior, at the same time, maintaining their mechanical stability [55].

A responsive behavior of hydrogels makes them very attractive materials for wide specific applications in human health, drug delivery systems, in adsorption and separation processes, which were discussed in this chapter.

3 Synthetic Hydrogels and Their Impact on Health

3.1 Hydrogel Use in Human Health

Hydrogels are suitable materials for potential application in medicine, because of their properties similar to the living tissue (soft and rubbery consistency and low interfacial tension with water or biological fluids). Hydrogels are biocompatible due to their great water-sorption capacity, which results in weak interactions with the extracellular-fluid components. Water absorption has an important role in maintaining the strength, durability, and creep resistance of biomaterials, which may be injured by hydrolytic degradation. In these cases, the surface has to possess different hydrophilic polar groups, usually derived from hydrophilic coatings and grafted polymers [56]. Hydrogels are very well tolerated in vivo when implanted. They can be easily tailored to suit many functions of prosthetics in contact with blood or tissues.

Hydrogels have been investigated for replacement blood vessels and chemical valve [57], wound dressing and implant materials [6, 57–59]. They have been applied for rhinoplasty [60, 61], breast implants [62], soft contact lenses [63–65], and a variety of other related uses.

The field of tissue engineering required new artificial organs and tissues and recognized the hydrogels properties as a scaffold material. The term “tissue engineering” is associated with replacement of various fractions of tissues or the whole tissue by using a combination of cells and engineering methods. Hydrogels structurally resemble the extracellular matrix of the human body and their 3D-structure organized cells and offer stimuli to direct the creation of new tissues [66]. Advances in hydrogel systems provide great new possibilities for application as model biological structures and in tissue regeneration [67]. The composite macroporous PEG hydrogel scaffolds with ordered, interconnected pores provided mechanical stability and potential to cytokines/chemokines depot, while an infused collagen matrix, as a tissue engineering platform, supporting intra-scaffold migration of loaded T cells and dendritic cells was tested in vitro [68]. The injectable, cytocompatible, and bioresorbable hydrogels based on PNIPAM and hydrolyzable lactone ring and epoxy pendant groups showed mesenchymal stem cell viability for 7 days and present a promising alternative for cell delivery [47].

Magnetic resonance imaging (MRI) was applied to overcome the conventional therapeutic approaches such as chemotherapy, radiation therapy, or surgical treatment. The MRI-monitored long-term therapeutic hydrogel system (MLTH) based on poly(organophosphazene) hydrogel was developed as an alternative approach for brain tumor therapy [69]. A novel core-shell nanogel composed by coating the Ag–Au bimetallic nanoparticle core, with a thermo-responsive PEG hydrogel as shell and semi-interpenetrating targeting ligands of hyaluronic acid chains into the surface networks, was investigated [70]. The synergistic effect of this nanogel in combination with the local specific chemotherapy with external photothermal treatment significantly improves the curing. A long-term theranostics hydrogel system which consisted of three major parts: thermosensitive/biodegradable poly (organophosphazene) hydrogel, PEGylated cobalt ferrite nanoparticles with low cytotoxicity and paclitaxel, was developed in vitro for paclitaxel sustained release [71]. The technology based on polyacrylamide nanoparticles covalently linked to Coomassie Blue molecules enables color-guided tumor resection in real time and can serve as a great help for the cancer diagnosis [72].

Integration of intelligent biomaterials into micro- and nano-electromechanical-based systems is one of the most promising ways in development of better diagnostics and treatment systems for pathophysiological conditions [73].

3.2 Hydrogel Use in Pharmacy

One of the major areas involving polymeric hydrogels is pharmacology. Different types of hydrogels, especially those physiologically-responsive, have been investigated for pharmaceutical applications. The applications started with implants composed of biostable polymeric matrices aimed at sustaining the release of entrapped drugs. The latest research in hydrogels, ranging from the type of stimuli (pH, temperature, biomolecules, pressure, ionic strength, electrical impulses, ultrasound, magnetic fields, and light) with different degrees of success for pharmaceutical and medical applications, have been described in literature [4, 74]. A number of controlled drug delivery systems (DDS) have been developed to prolong and control the drug release for a period of time for improving curing efficiencies. The hydrogel-based DDS have revolutionized the pharmaceutical world. The drug delivery systems based on synthetic non-biodegradable polymers (poly(methylmethacrylate), poly(2-hydroxyethyl methacrylate), poly(acrylic acid) (PAA), poly(*N*-isopropylacrylamide) (PNIPAM), and poloxamer), beside DDS based on biodegradable natural and synthetic polymers (polyesters, poly(lactic acid), poly(D,L-lactide/glycolide), poly(ϵ-caprolactone)), have been analyzed in detail [75].

Smart hydrogel application in contemporary medicine has growing importance, due to their ability to design the desired properties. The drug release from superporous chitosan/poly(vinyl alcohol) hydrogels was sustained for 6 h [55]. These studies showed that chitosan-based superporous hydrogels may be used as a gastroretentive drug delivery system for rosiglitazone maleate. Biocompatible poly (*N*-isopropylacrylamide/itaconic acid), P(NIPAM/IA), hydrogel was investigated for

controlled release of salicylic acid [25] and as support for lipase immobilization [76]. New technologies involved in hydrogels enable more localized and modulated delivery of a steroid methylprednisolone [77]. The potential use of NIPAM-based hydrogels was studied for modified release of drugs, e.g., paracetamol [78], phenacetin [79], ibuprofen [80], naproxen [81], piroxicam [81], ellagic acid [82], and bovine serum albumin [7]. Kou et al. studied release of model drug phenylpropanolamine from poly(hydroxyethyl methacrylate/methacrylic acid) hydrogels [35]. The injectable hydrogel based on PEG served as a potential candidate for locally controlled release of methylprednisolone in perineal and intraparenchymal spaces of the spinal cord [83].

Chemically cross-linked hydrogels were intensively investigated to protect and deliver active substances. Many academic papers and patents about possible applications of hydrogels in drug delivery have been published, but, only a few have resulted in commercial products. The most important criterion that had to be satisfied is the combination of active substances with the polymeric carrier, complemented by drug release profiles. Some of the issues that should be systematically included to define strategies for practical therapeutic applications of hydrogels involve [84]:

- The counteractive action of natural defenses, the action of the complement, and the risk of immune-type alteration of surrounding tissues
- Chemical and physico-chemical interactions between more or less amphiphilic and electrostatically charged foreign polymeric surfaces, systems with cell membranes and circulating macromolecules, or chemical species like proteins, lipids, and phospholipids
- The achievement of characteristics compatible with the required therapeutic action
- The difficulty to control the limiting effects of the great ratio between surface and volume on the loading of nano-sized systems and the release of the load.

3.3 Hydrogel Use in Cosmetics

In the last decades, there are many requirements for more effective cosmetic products for improvement in skin appearance and also skin health that resulted in the introduction of more active ingredients. All of the active ingredients for skin cleansing, protecting, renewing, restoring, and rejuvenating are very labile to air, light, heat, moisture, metal ions, oxygen, and base and easily decompose into biologically inactive compounds [40]. Lots of new cosmetic products are based on smart delivery system in order to protect cosmetic ingredients into hydrogel matrices. One of them is engineered poly(vinylpyrrolidone) (PVP) aqueous hydrogel used for “beauty masks” to hydrate the skin, restore its elasticity, and promote anti-aging actions (Pecogel by Phoenix Chemicals Inc.) [85]. PVP-based hydrogels are suitable for cosmetic products, such as hair care products, waterproof sunscreen products, or mascara [86]. Their ingredients contain patented hydrogels based on biocompatible vinylpyrrolidone polymers or copolymers and hydrophilic poly(urethane). These materials have unique rheological

and film-forming properties and the ability to complex with a wide range of organic molecules (dyes, anti-microbials, and UV absorbers). Parente et al. presented hydrogel formulations with prevalently elastic rheological behavior based on covalently cross-linked PAA hydrogels, hydrophobically modified by the incorporation of long-chain alkyl (C10–C30) acrylates. This bioadhesive hydrogel was developed for skin application, using caffeine as a model active ingredient [87].

In some of the commercially available products, the moisturizing action of organic polymeric gels is coupled with more complex drug delivery systems developed for release of biomolecules like vitamin C or B3 such as hydrogel face masks by Fruit & Passion Boutiques Inc. [88]. The pH-sensitive P(MAA/EGMA) hydrogel microparticles were prepared and applied as smart delivery carriers for cosmetically active ingredients such as arbutin, adenosine, and niacinamide [40]. At low pH condition (pH = 4), the cosmetic ingredients cannot be released from the P(MAA/EGMA) hydrogel particles, due to the collapsed hydrogel network, so in this way, the ingredients are protected. When the cosmetic ingredient-loaded hydrogel particles are applied to the skin (where the pH is always around pH 6), the surrounding pH increases, leading to release of the cosmetic ingredients from the particles and their absorption through the skin. The other example is method of making skin adhesive hydrogel based on high molecular weight water-soluble PVP, having pyrrolidone groups ring opened, and poly (ethyleneimine), useful for wound/burn dressing, or cosmetic face mask/nail wrap [89].

3.4 Safe and Toxicity of Hydrogels for Humans

Many efforts have been made to design hydrogel-based DDS to reduce undesirable systemic toxicity of drugs and dose strength. Numerous clinically approved hydrogels are available on the pharmacies. Biocompatibility of a polymeric hydrogel with the surrounding tissues is the first criterion for use in DDS. The requirements for hydrogel systems include the materials in which precursors and the soaked products are non-cytotoxic. Important parameter for the biocompatibility assessment implies viability of cells and their proliferation. In situ hydrogels are exclusively used for cell encapsulation [66]. The main features for cell encapsulation in a hydrogel matrix include the application of water-based processes with hydrophilic precursors, without organic solvents which can damage the cells. The overall structure should fit well for cell proliferation and must degrade into non-toxic substances at a specific rate to that of growing tissue [90]. The researchers usually determine the cell viability and cell proliferation from the cytotoxicity test. The relative cell viability testing of the synthesized injectable carboxybetaine hydrogels demonstrated that hydrogels are potential scaffolds for cell encapsulation and proven candidates in drug compound screening for hepatotoxicity and drug efficacy [91].

Biomedical applications of synthetic hydrogels were initially hindered by the toxicity of unreacted monomers and cross-linkers, low biodegradability, and limitations of hydrogel formation under physiological conditions, but not with the polymer network itself [20]. The reactants used for the hydrogel synthesis (monomers, cross-linkers, initiators, inhibitors, and solvents) [91–98] are molecules with reactive

functional groups, usually hazardous and toxic, some of them with neurotoxic, carcinogenic, teratogenic, or mutagenic effects. Repeated or prolonged exposure to these substances may cause skin sensitization, an allergic reaction, target organ damage, or irritation. After the polymerization process, reactive molecules formed permanent covalent bonds in the stable polymer networks and became safe for human utilization. Synthesis of hydrogels with a minimum content of residual reactants and unwanted side reaction products is a necessary precondition for their human applications. For this reason, it is important to remove them from synthesized hydrogels by rinsing out with appropriate solvents and then analyze them. The residual monomer content of up to 0.5% and even up to 1.0% or more is often found in polymers produced on an industrial-scale application [23, 34]. After poly (hydroxyethyl methacrylate/methacrylic acid) hydrogel synthesis, residual reactants were removed and washed with distilled water [35]. The synthesis was carried out by radical polymerization with different content of ethylene glycol dimethacrylate (EGDM) as cross-linker [33]. Synthesized P(AA/MAA) hydrogels were treated with acetonitrile, while PNIPAM and P(NIPAM/HPMet) hydrogels were treated with methanol for removing the unreacted monomers and cross-linkers. Quantities of residual reactants after synthesis of P(AA/MAA) and NIPAM-based hydrogels also confirmed successful polymerization processes [33, 34, 99]. To reduce the level of residual reactants, chemical and physical methods are applied and determined to use the two most common equipment, gas chromatography (GC) and high-performance liquid chromatography (HPLC) [100]. Reduction of residual methylmethacrylate monomer in acrylate dental prosthetics based on poly (methylmethacrylate) and poly(methyl methacrylate/acrylamide) was achieved by polymer boiling in water [101, 102]. Residual monomer content of superabsorbent hydrogels was minimized via alteration of initiating system [103].

Hydrogels have weak mechanical properties which limit their use in tissue engineering scaffolds, especially in load bearing tissue matrices and wound sealants. Nanocomposite hydrogels with high elongations and mechanically improved toughness were synthesized by photo-cross-linking PEO–PPO–PEO triblock copolymer diacrylates (Pluronic F127 diacrylate) in the presence of silicate nanoparticles, Laponite [59].

The difficulty to load the drug into hydrogel matrices is the prior issue which needs to be considered for enhancing the hydrogel applications as drug carriers. The limitations in hydrogel applications are moisture retention for their stability and proper functioning, which is required for the sterility, transportation, and storage [66]. Emerging knowledge in polymer chemistry and increased understanding of biological processes resulted in design of adaptable materials and minimally invasive therapies [20].

4 Synthetic Hydrogels and Their Impact on the Environment

Synthetic hydrogels' impact on the environment is reflected in two ways: their application for the removal of pollutants (heavy metals, dyes, radioactive and rare earth elements) by adsorption processes and as systems for the controlled release of agrochemicals (pesticides and fertilizers) [17].

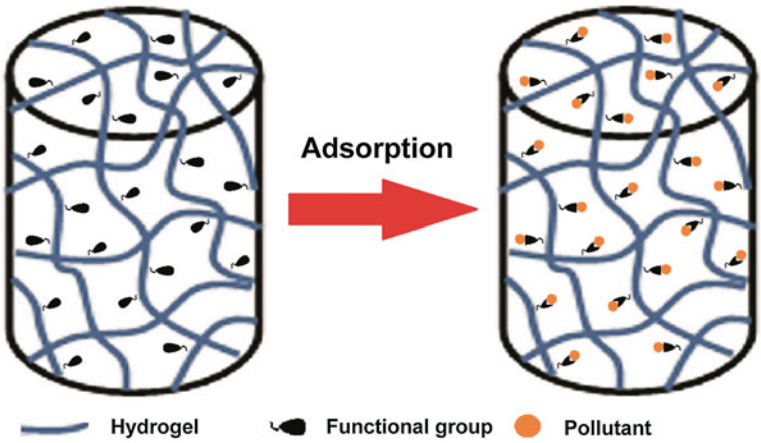

Fig. 1 Schematic review of pollutant adsorption from aqueous solutions. (Reprinted with permission from [17]. Copyright © 2017, Faculty of Technology, University of Niš, Republic of Serbia)

Heavy metals, dyes, and radioactive elements are present in the effluents of paper and pulp industries, textile industries, nuclear power plants, leather tanning, and manufacturing of batteries, ores, steel, petrochemicals, and fertilizers [104–107]. Water pollution with mentioned pollutants represents a serious problem because of their toxic effects on the living world and ecosystems [11, 108, 109]. Adsorption or biosorption is an effective and low-cost method for removal of pollutants from diluted aqueous solutions [110]. Synthetic hydrogels especially hydrogels sensitive to external stimuli can be applied as adsorbents [108, 111]. High absorption and adsorption capacity, ease of handling, and regeneration ability enable applications of hydrogels for the treatment of contaminated water [15, 112]. The adsorption of pollutants from aqueous solutions onto the hydrogels is schematically presented in Fig. 1.

Agrochemicals are bioactive agents widely used to improve crop production, but their conventional and inadequate application exerts adverse effects on humans and environment. Hydrogels are used as carriers for pesticides and fertilizers. They are used to release agrochemicals in a controlled manner [113, 114].

4.1 Adsorption of Heavy Metals and Radioactive and Rare Earth Elements

Smart hydrogels, i.e., stimuli-responsive hydrogels, are widely used for removal of heavy metals from aqueous solutions by adsorption [115–117]. Hydrogels can form chelates with heavy metal ions, because they act as a Lewis base, donating a pair of electrons. In the hydrogel structure, functional groups (carboxyl, ester, amino, hydroxyl, or sulfonyl group) or oxygen, nitrogen, sulfur, or phosphorus atoms are

the electron donors. Therefore, hydrogels remove heavy metal ions from aqueous solutions by electrostatic interactions [118]. One of the adsorption mechanisms of these pollutants onto hydrogels can be also ion exchange [16, 117]. The regeneration ability of the hydrogel significantly decreases the costs of heavy metals adsorption processes. Regeneration of stimuli-responsive hydrogels is carried out at a temperature higher than LCST or in a very acidic environment [108, 119, 120].

Hydrogels synthesized from AA and PVP, PVA, NIPAM, or PEG represent suitable adsorbent materials for heavy metals [108, 111, 117, 119, 121]. The adsorption of Fe(III), Cu(II), and Mn(II) ions onto poly(vinylpyrrolidone/acrylic acid) (PVP/AA) hydrogels depends on the composition of the adsorbent and pH of the surrounding medium. PVP/AA copolymer with reactant molar ratio of 80/20 mol% showed good adsorption properties toward metals [108]. In the work of Al-qudah et al., poly(vinyl alcohol)/acrylic acid (PVA/AA) hydrogels synthesized by gamma irradiation were used for removal of Zn(II), Co(II), and Mn(II) ions. The adsorption is a favorable and pH-dependent process. At low pH values, adsorption capacity of the PVA/AA hydrogels is reduced due to protonated alcohol and carboxylic groups. The increase of environmental pH leads to higher adsorption ability of hydrogels. Adsorption of heavy metal ions from aqueous solutions can affect the surface characteristics of the hydrogel, temperature, contact time, and the initial concentration of pollutants. PVA/AA hydrogels have high adsorption capacities for heavy metals (152–388 mg/g) [119]. A suitable adsorbent for heavy metals was obtained by glow-discharge plasma electrolysis technique from reactants PEG and AA. Chemical complexation and ion exchange were probably the main mechanisms for removal of Pb(II), Cu(II), and Cd(II) ions by PEG/AA hydrogels. Desorption ratio of heavy metal ions after third regeneration adsorbent materials with nitric acid was above 88%. Protonation of carboxyl groups leads to desorption of heavy metal ions from the surface of the PEG/AA hydrogels [117]. Other authors have investigated the possibility of using the P(NIPAM/AA) hydrogel as the adsorbent for Cu(II), Mn(II), Cr(VI), and Fe(III) ions. Important metal-binding sites in the structure of P(NIPAM/AA) hydrogels were carboxylic and amide groups [111, 117, 121]. Chen et al., based on kinetic data, concluded that the adsorption of Cu(II) ions onto P(NIPAM/AA) hydrogels takes place by surface reaction and intra-particle diffusion [121].

The presence of salt and competitive ions can influence the adsorption behavior of hydrogels. In the work of Antić et al., increase in NaCl concentration decreases the adsorption capacities of poly(2-hydroxyethyl acrylate/itaconic acid) (P(HEA/IA)) hydrogels for Cd(II) ions. The adsorption capacity of Cd(II) ions is decreased in the presence of Ni(II) or Pb(II) ions by 8.51% and 24.5%, respectively [115]. Multicomponent heavy metal ion adsorption for "smart" hydrogels based on 2-hydroxyethyl acrylate (HEA) and acrylamide-2-methylpropane sulfonic (AMPS) acid or maleamic acid (MALA) was investigated [116, 122]. The reason for this analysis is that in industrial wastewaters, generally, various heavy metal ions exist. Removal capacities of poly(2-hydroxyethyl acrylate/acrylamide-2-methylpropanesulfonic acid), P(HEA/AMPS), copolymer hydrogel for different heavy metal ions decrease in the following order: Cr(III) > Fe(III) > Cu(II) > Cd(II) > Pb(II).

Rate-limiting step in adsorption of metal ions was chemisorption and partly physisorption [116]. Based on the results, Wu et al. suggested that Pb(II), Cd(II), Ni(II), Cu(II) ions were removed from aqueous solutions onto poly(2-hydroxyethyl acrylate/maleamic acid), P(HEA/MALA), hydrogels by electrostatic interaction, chelation, and ion-exchange. In the multicomponent adsorption, P(HEA/MALA) hydrogel showed the highest capacity for Pb(II) ions [122].

Besides copolymer hydrogels, for removal of heavy metals, homopolymer hydrogels were applied. One example is the temperature-sensitive homopolymer PNIPAM. Adsorption performance of PNIPAM hydrogel significantly depends on environmental temperature. At temperature lower than LCST, PNIPAM exhibits higher adsorption capacity toward Pb(II) ions (120 mg/g at 23 °C). Desorption of heavy metal ions appeared at temperatures higher than LCST of PNIPAM due to reduced adsorption surface and volume of hydrogel [120]. PNIPAM synthesized by radical polymerization with cross-linker EGDM have been used as adsorbents for removal of following adsorbates: Mn(II), Cr(VI), Pb(II), and Fe(III) ions [123].

Tokuyama and Iwama proposed the method which can be applied for separation of heavy metals, so-called temperature-swing solid-phase extraction (TS-SPE). The method is based on the complexation of metal ions and an extractant in the solutions, and then the adsorption of the formed complex onto the PNIPAM precipitate. Hydrophobic interaction is established between metal-extractant complex and homopolymer. By lowering the temperature, adsorbed complexes are released. Adsorption takes place at a temperature higher than LCST of PNIPAM [124, 125]. In Fig. 2 schematic review of TS-SPE methods for separation of target pollutants, heavy metals or rare earth and radioactive elements is shown.

TS-SPE has been used for adsorption of the Cu(II) ions onto the hydrogel PNIPAM in the presence of anionic surfactants sodium *N*-dodecylbenzenesulphonate (SDBS) or *N*-dodecylbenzenesulfonic acid (DBS) [124].

Composite hydrogels are also representing adsorbent materials for heavy metal ions. Nanocomposite hydrogels consisting of wheat bran-g-poly(methacrylic acid) and clinoptilolite (WB-g-PMAA/CLINC) showed adsorption potential for the following heavy metal ions: Pb(II), Cu(II), Cd(II), and Ni(II) ions [126]. Grafting copolymerization of sodium alginate, sodium acrylate, and a medical stone, composite hydrogels was obtained. In addition to adsorption properties, the composite hydrogels are sensitive to the pH change and behave like superabsorbent polymer. The adsorption capacity of the synthesized composite hydrogels for Ni(II), Cu(II), Zn(II), and Cd(II) ions is higher compared to the active carbon and medical stone [127]. Pb(II) ions are removed by hydrogel composite based on linear low-density polyethylene, AA, starch, and the organo-montmorillonite (LLDPE-g-PAA-*co*-starch/OMMT). For adsorption of heavy metal, probable responsible mechanism was physical adsorption, ion exchange, and the chelation between the adsorbate and the carboxyl and hydroxyl groups of the composite. The maximal removal amount of heavy metal is reached at a pH 4.5, 430 mg/g [128].

SPE method can be applied in case of radioactive and rare earth elements [125, 129]. In(III) ions are effectively removed from the aqueous solution by hydrogel PNIPAM with organophosphorus extractant *N*-octyl phosphate (OP).

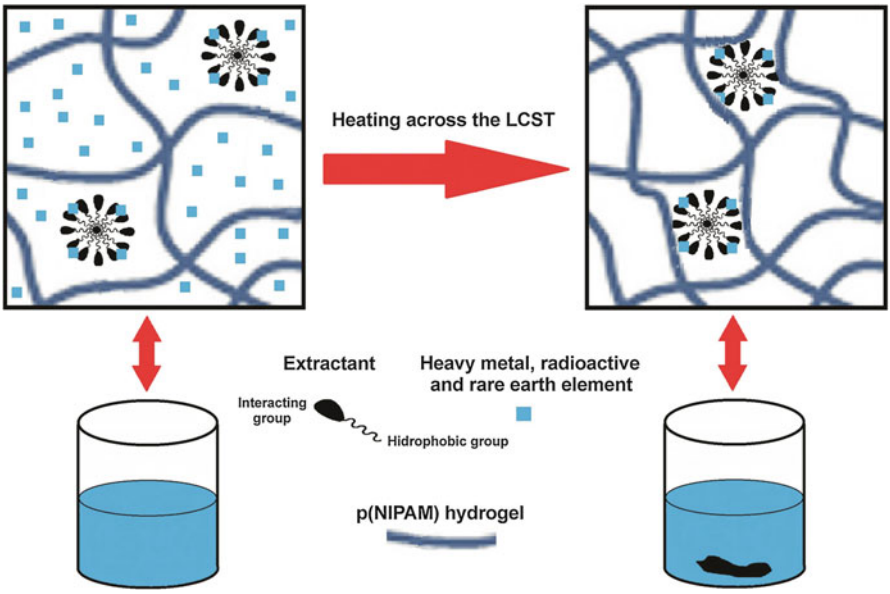

Fig. 2 Schematic review of TS and SPE techniques for adsorption of heavy metals or radioactive and rare earth elements. (Reprinted with permission from [17]. Copyright © 2017, Faculty of Technology, University of Niš, Republic of Serbia)

The lower amount of In(III) ions were adsorbed onto hydrogel without an addition of OP extractant. The mutual separation of the In(III) and Zn(II) ions was investigated by the SPE method. The results showed that the In(III) ions are significantly higher adsorbed onto PNIPAM precipitate from the binary and single solution. Therefore, extractant plays the role of a separator after which the In(III) ions are selectively removed from aqueous solution by homopolymer [125].

Hydrogels of P(NIPAM/IA) and poly(acrylic acid/benzo-18-crown-6-acrylamide), P(AA/B18C6AM), showed excellent adsorption properties toward radioactive Cs(I) ions [11, 130]. At temperatures below LCST, Cs(I) ions were adsorbed onto P(NIPAM/IA) hydrogels [130]. Removal of Cs(I) ions by the hydrogel P(AA/B18C6AM) occurs through electrostatic interactions of metal with the carboxylic groups of AA and the formation 2:1 "sandwich" complexes B18C6AM-Cs(I). High adsorption capacity of P(AA/B18C6AM) hydrogel for Cs(I) ions was achieved within 30 min [11].

Anirudhan et al. have tested adsorption efficiency of the composite poly (methacrylic acid)-grafted-cellulose/bentonite, PMAA-g-cell/Bent, for removal and recovery of Th(IV) ions from the solution. The maximum removal efficiency was obtained at a pH of 5 (99.7%). Desorption of Th (IV) ions from composite may be carried out by addition of 0.1 M solutions of nitric acid [10].

Homopolymer PAA, synthesized by radical polymerization, demonstrated good adsorption behavior for radioactive elements. In the process of complexation at pH

4, significant amount of U(VI) ions was removed by PAA hydrogel, 445.11 mg/g. After fifth adsorption/desorption cycles, sorption capacity of the hydrogel is slightly decreased (by 9.09%) [131]. Poly(acrylamidoxime/2-acrylamide-2-methylpropane sulfonic acid) hydrogel can be used as adsorbent materials for removal of U(VI) ions [129].

4.2 Adsorption of Dyes

Dyes represent complex aromatic compounds of different structures that are stable and almost non-biodegradable [109]. In the literature, most studied was removal of cationic and anionic dyes from the aqueous solutions by hydrogels [132–134]. In recent years for the adsorption of dyes, hydrogel composites were also used [109, 135–137]. Table 1 shows various hydrogels used for removal of dyes and their adsorption capacity or removal efficiency.

During the purification of wastewater containing dyes, efficiency of the process depends on the interaction between hydrogels as adsorbent and dyes. In a paper by Fradj et al., between PAA hydrogels and cationic dyes Basic Blue 9 (Methylene Blue) and Basic Blue 17 (Toluidine Blue), mainly electrostatic interactions have been established. The increase of temperature had negative effects on formed PAA-dye complex [138]. Hydrogel adsorption potential of PAM was investigated, wherein the model substances were Direct Red 31 and Reactive Orange 20 dyes. Also, PAA is used as the adsorbent. PAM hydrogel has a higher adsorption capacity toward anionic dyes, which is attributed to presence of amide groups as well as a higher specific surface area of the hydrogel. Amide groups at lower pH solution

Table 1 Comparison of adsorption capacity or removal efficiency of different hydrogels for dyes

Hydrogel	Dye	Adsorption capacity (mg/g) or removal efficiency (%)	References
PAA	Direct Red 31, Reactive Orange 20	143.88 mg/g for Direct Red 31 and 19.86 mg/g for Reactive Orange 20	[132]
PAM	Direct Red 31, Reactive Orange 20	155.28 mg/g for Direct Red 31 and 92.4 mg/g for Reactive Orange 20	[132]
P(AM/AA)	Basic Blue 9	1315 mg/g	[133]
P(AM/AA)	Reactive Red 239	44.19 mg	[134]
P(AM/MA)	Basic Blue 12	58.86%	[139]
P(MAA/AMPS)	Basic Yellow 28, Basic Red 46	98.8% for Basic Yellow 28 and 96.4% for Basic Red 46	[140]
PAM/Lap	Basic Blue 12, Basic Blue 9, Basic Violet 1	>90%	[135]
AM/AMPSNa/MMT	Basic Red 2, Brilliant Cresyl Blue	484.2 mg/g for Basic Red 2 and 494.2 mg/g for Brilliant Cresyl Blue	[109]

more protonated than carboxyl groups of the PAA, which resulted in stronger electrostatic interactions PAM with anionic dyes [132].

Copolymer hydrogels of poly(acrylamide/acrylic acid), P(AM/AA), synthesized by process described in the work of Mekewi et al. with a different molar percent ratio of AM/AA (80/20, 50/50, 20/80) are characterized by high adsorption of dye Basic Blue 9. Increasing the molar feed percentage of the monomer AM leads to increase of the adsorption capacity (from 950 to 1315 mg/g), but it reduces the adsorbent reproducibility [133]. Dye Reactive Red 239 (Remazol Red 3BS) is another adsorbate applied in the investigation of adsorption ability copolymers P(AM/AA) [134]. The reaction of a radical polymerization of acrylamide with monomer mesaconic acid (MA) was prepared adsorbent for removal of dye Basic Blue 12 (Nile Blue chloride). Interaction mechanisms of dye and hydrogel of poly(acrylamide/mesaconic acid), P(AM/MA), may be hydrogen bonding, hydrophobic interactions, dipole–dipole, and dipole-induced dipole interactions. Copolymer P(AM/MA) reaches the removal percent of dye Basic Blue 12 of 58.86% [139]. Nesic et al. investigated the effect of single and binary system dyes Basic Yellow 28 and Basic Red 46 on the adsorption characteristics of the hydrogels of poly(methacrylic acid/2-acrylamide-2-methylpropane sulfonic acid), P(MAA/AMPS). Copolymerization of MAA and AMPS has achieved greater adsorption ability to applied dyes compared to homopolymers PMAA and PS-PAMPS. The results indicate that better removal was obtained by adsorption dyes in the binary system onto copolymer hydrogels P(MAA/AMPS), maximal values of 98.8% for Basic Yellow 28 and 96.4% for Basic Red 46 [140].

Semi-IPN type hydrogels synthesized by polymerization of acrylic monomers (AA and acrylamide) in water with sodium alginate have an affinity for dyes Basic Red 9 (Basic Fuschin) and Basic Violet 1 (Methyl Violet) dyes. The process of adsorption of dyes is exothermic. Basic Red 9 dye is adsorbed in larger percentage onto hydrogel type SIPN4 (1 wt% *N′N′* methylene bisacrylamide, 4 wt% of sodium alginate and AA/AM ratio 5:1) [141].

Hydrogel composites with clay having good physical properties (toughness, heat resistance, and transparency) and allow a variety of reactions on their surface. Composites are increasingly used for removal of dyes from aqueous solutions. One example of nanocomposites is poly(acrylamide/laponite) (PAM/Lap) which were synthesized by in situ free radical polymerization of the monomer AM in an aqueous solution with clay. Basic Blue 12, Basic Blue 9, and Basic Violet 1 were removed with the synthesized nanocomposites. Increase of clay amount from 25 to 40 wt% in the hydrogel compositions causes a significant increase in the removal capacity of dyes. Higher capacity is a result of the amount increase of negative charge on the surface of the hydrogel composite and therefore the enhanced interaction between dyes and adsorbent. The authors suggested that possible interaction mechanisms are ion exchange, hydrogen bond, and hydrophobic interactions. Removal percent of dyes by hydrogel prepared with 40 wt% clay are above 90% [135]. For hydrogel-clay nanocomposites preparation, natural clays (kaolin and montmorillonite) were used [109, 136, 137]. Nanocomposite synthesized by in situ copolymerization of AM and 2-acrylamide-2-methylpropanesulfonic acid sodium salt (AMPSNa) in

water with montmorillonite (MMT) clay exhibits better swelling and adsorption characteristics compared to hydrogel copolymers poly(acrylamide/2-acrylamide-2-methylpropanesulfonic acid sodium salt), P(AM/AMPSNa). The diffusion of aqueous solutions of dyes Basic Red 2 (Safranin-T) and Brilliant Cresyl Blue (CI no name) onto the composite is a non-Fickian character. The equilibrium adsorption capacities of nanocomposite hydrogel AM/AMPSNa/MMT for applied dyes is reached for about 10 min [109].

4.3 Hydrogels for Controlled Release of Agrochemicals

Approximately 90% of applied agrochemical does not exert its biological effect toward its target, which was partly due to the method of application. Toxic substances such as agrochemicals can reach the surface and groundwater through runoff from arable land, leaching, or irrigation. Using agrochemical-controlled systems based on hydrogels prevents the photodegradation, evaporation, and leaching of agrochemicals, and therefore lowering the environmental problem [4, 114]. Superabsorbent hydrogels have other uses in agriculture: for improving water retention in the soil and providing water for plant growth [142, 143].

Two methods of preparing a formulation based on hydrogels as agrochemical-controlled systems are distinguished: (1) the absorption of an agrochemicals solution in already synthesized hydrogel and (2) the synthesis of the hydrogel in the agrochemicals solution. In the first method after absorption of chemicals, removal of water is needed, while the second method is followed by drying up [4, 18, 143–145].

In the paper of Saraydin et al. as model, the following substances were used: herbicide sodium 2,2-dichloropropionate (dalapon) and fertilizers ammonium nitrate, potassium nitrate, and ammonium sulfate for testing agrochemical-controlled systems based on the synthesized copolymer hydrogels by radiation (according to the second method). The release of applied agrochemical from copolymers of poly(acrylamide/itaconic acid), P(AM/IA), and poly(acrylamide/crotonic acid), P(AM/CA), is a result of water penetration within the polymer matrix, i.e., swelling [144, 145]. Schematic representation of pesticide or fertilizer release controlled by swelling is shown in Fig. 3.

As carrier for ammonium nitrate, hydrogels based on AM, AA, hydroxypropyl acrylate (HPA), and glycidyl methacrylate (GMA) were prepared by free radical copolymerization process. The release of agrochemicals depends on the loading amount and composition of the hydrogel. Increasing the percentage of ammonium nitrate loading from 180 to 360 wt% causes increase in rate of agrochemicals release. The difference in concentration of solute between the hydrogel and the medium leads to release of ammonium nitrate. Diffusion of fertilizer outside affects the electrostatic repulsion between the carboxylic groups (COO^-) and NO_3^- ions in the hydrogel [146].

PAM homopolymer porosity was achieved by hydrogel synthesis with calcium carbonate microparticles. By treatment of hydrogel by hydrochloric acid, calcium carbonate and the remaining compounds were removed from hydrogel surface. PAM

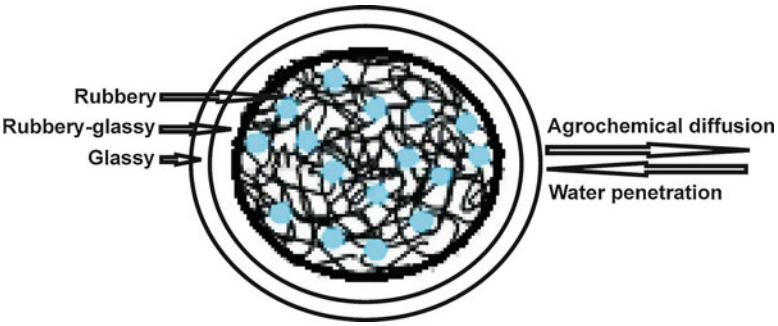

Fig. 3 Schematic review of agrochemical release from polymer by water penetration. (Reprinted with permission from [17]. Copyright © 2017, Faculty of Technology, University of Niš, Republic of Serbia)

hydrogels were loaded with model fertilizer potassium nitrate, and the impact of calcium carbonate content, cross-linker concentration, and amount of loading on the release of agrochemicals was investigated. It is obvious that with a decrease of cross-linking, i.e., concentration of cross-linkers methylenebisacrylamide (MBA), the percentage of potassium nitrate release from hydrogels increases. Reduction of loading and calcium carbonate amount has the opposite effect on agrochemicals release [147].

In the work of Rudzinski et al., hydrogel copolymers based on methyl methacrylate (MMA), methacrylic acid (MAA), and 2-hydroxy methacrylate (HEMA) were used for encapsulation of cypermethrin (pesticide). Three types of hydrogel were synthesized, I, MMA/MAA 25/75 mass%; II, MMA/MAA/HEMA 50/50/0.01 mass %; and III, MMA/MAA 75/25 mass%, with EGDM as a cross-linker. Cumulative release of pesticides from copolymers II and III is considerably fast at the beginning, while with copolymer I slower and prolonged release of the agrochemical was achieved [148].

Agrochemical-controlled systems for potassium nitrate were prepared by graft copolymerization of PAM onto carboxymethylcellulose (CMC) or onto CMC and PVA [18, 114, 149].

5 Conclusion

This chapter provides an effort to highlight diverse applications based on many publications in few different fields. From literature overview, a lot of inventive polymerization route for hydrogel synthesis was presented. The porous hydrogel network shows selectivity for proteins, enzymes, drugs, dyes, pigments, or metal ions, which can be easily incorporated into hydrogels for many adequate applications. Over the past decades, significant progress has been made in development of hydrogels as functional biomaterials, because of many of their desirable properties,

i.e., low toxicity and good biocompatibility. Their potential for application in human health and tissue engineering and advances in pharmaceutical field, drug delivery systems, and cosmetic treatments have been analyzed. Aspect of safety and potential toxicity of synthetic hydrogels was considered. In this chapter, studies in the application of synthetic hydrogels as adsorbent material for removal of pollutants, dyes, heavy metals, and radioactive elements as well as for controlled and sustained release of agrochemicals and their impact on the environment were also summarized.

6 Future Scope

Nowadays, hydrogels are excellent contemporary materials for scientists and researchers with great advances in their formulations and applications.

The hydrogels already have practical application in many products, i.e., contact lenses, hygiene products, and wound dressing, but commercial hydrogel products in tissue engineering and drug delivery systems are still limited. Future development of synthetic hydrogels provides many innovative materials and technologies to overcome the disadvantages of conventional therapy. Many drug delivery systems based on hydrogels have been designed, some of them patented, but only a few have marketing authorization. Despite all beneficial properties, there are still several challenges to overcome for clinical translation. One of the limits in further commercialization is their high production cost. The hydrogel synthesis and in vitro tests seem easy in relation to in vivo application and require new wider testing before commercial applications. Their further development and production may reduce the price and enable wider application in human health.

Advances in hydrogel synthesis and processing have led to a new generation of dynamic systems, which are capable of responding to biological signals and artificial triggers with good precision. The sophisticated level of these new hydrogel based materials is reflected in new developments in, e.g., shape memory and self-healing hydrogels.

Also, the application of hydrogels as adsorbent material is very promising and at the beginning of development and exploitation. In recent years, superabsorbent hydrogels networks with tailored functional groups have much attention for removal of different pollutants from aqueous solution. Hydrogels have applications in arid regions for improving water retention in sandy soils and the water supply to plants. There are many investigations aimed at developing novel hydrogels with high adsorption capacity and fast adsorption rate for different kinds of pollutants. But, selective adsorption for a specific pollutant may be interesting in the future research. Many experiments have satisfactory results in the hydrogel application as adsorbents, but they were carried out in laboratory batch and small-scale column tests only. There is little data available for removal of pollutants in presence of other available substances. In the future works, it will be needed to predict the adsorption processes in real industrial effluents and the investigation in pilot–plant studies to examine their feasibility at industrial level.

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Polysaccharide-Based Superabsorbents: Synthesis, Properties, and Applications

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Abstract

Traditional absorbent hydrogels are based on the copolymerization of petroleum-based synthetic vinyl monomers such as acrylic acid, methacrylic acid, and acrylamide derivatives. Nevertheless, these materials are usually expensive, poorly degradable, and non-environmentally friendly. On the contrary, natural polysaccharides display significant advantages such as availability, low production cost, nontoxicity, biocompatibility, and biodegradability. Accordingly, polysaccharides emerge as an interesting sustainable alternative to traditionally employed polymers. In addition, polysaccharides can easily form hydrogels by chemical or physical crosslinking (including hydrogen bonding and ionic interactions) or a combination of both, which makes the crosslinking of natural polysaccharides a versatile and promising approach for superabsorbent hydrogel (SAH) production. Therefore, in the last years, numerous polysaccharides including starch, cellulose, alginate, chitosan, and guar gum, among others, have been employed in SAH fabrication. Polysaccharide-based SAHs have been used in agriculture, hygiene products, waste treatment, crack mitigation in building applications, tissue engineering, and controlled release, for biomedical and soil conditioning applications. Despite of the evident commercial and environmental advantages of polysaccharide-based SAHs, they also display some drawbacks that make them continue appearing as a challenge research field. In this sense, although the biodegradability of polysaccharide-based hydrogels is a key characteristic for some applications because it avoids pollution-related issues and enables enhanced controlled release, at the same time, it could delay the development of longtime sustained release systems. Moreover, polysaccharide crosslinking leads to hydrogels with poor mechanical stability which is another associated disadvantage of these types of materials that needs to be overcome. Therefore an increasing amount of investigations about new synthetic approaches to improve the properties of polysaccharide-based hydrogels have been reported in the last years. In this chapter, the recent progress of this type of hydrogels is reviewed. The synthetic methods employed to obtain SAHs from the most common polysaccharides and the main properties of these materials with a special emphasis on swelling and mechanical properties are studied. Furthermore, the applications of SAHs have been summarized highlighting the most outstanding and promising uses.

Keywords

Polysaccharides · Hydrogels · Biodegradation · Water treatment · Chitosan

1 Introduction

Superabsorbent hydrogels (SAHs) are three-dimensional polymeric networks that are able to absorb and retain extremely high quantities of aqueous solutions without dissolution based on their highly hydrophilic nature [1]. SAHs are the most commercially known type of hydrogel, and their production implies about 80% of the

whole hydrogel production [2]. These attractive materials have been receiving an increasing attention in the last decades due to their interesting applicability in many fields. Nevertheless, the market for SAHs traditionally is focused on the hygiene and technical sectors [3]. Since the late 1980s, SAHs have been specially used in the manufacture of personal disposable hygiene products (baby diapers and sanitary napkins); however, in the last years, a wide range of applications, apart from hygiene products, have corresponded to technical SAHs [2]. Among these applications are noteworthy those in which SAHs act as micro-reservoirs for chemical substances which are released along the time and even under specific conditions such as changes of temperature or pH [4–6]. This approach has been specifically developed for agricultural use, as water reservoirs, soil conditioners, and controlled release systems for agrochemicals [6, 7]. In this sense, a long list of benefits of the uses of SAHs is demonstrated not only increasing the availability of water in the soil, reducing the evapotranspiration rate of the plants, and inducing higher growth rate but making decreased compaction, increasing the aeration of soil and the microbial activity, preventing erosion, improving fertilizer efficiency, and, thus, preventing the contamination of the underwater sources and reducing the effects of salinity, among others [2, 8].

Biocompatible SAHs have been exploited to many uses in biomedicine, such as for removing of body fluids during surgery [9] or for prolonging the retention of orally administrated drugs in the stomach or in the intestine [10]. When they are prepared in the form of microparticles, they have been specifically designed as superdisintegrant, in fast-disintegrating tablets [11], and as part of plugs and hemostatic or other medical devices [2]. These SAH microspheres could penetrate the intralesional vessels for transarterial embolization treatment of arteriovenous malformations [2].

Technical SAHs are also used for electrical purposes. Water-blocking tapes and cable coatings of SAHs are produced for covering communication and power cables and pieces exposed to seawater or underground water in order to prevent water from entering in case of outer coating damage [2]. More recently, the use of SAHs as multifunctional additives has been demonstrated to improve several properties of cement composites, including ductility, freeze–thaw resistance, and internal curing time [3]. In addition to the absorption of water and aqueous fluids, SAH networks are also capable of absorbing many molecular and ionic species. Based on this, SAHs have been used in separation processes and water treatment for removal of heavy metals and pollutants [12].

Due to the large range of advantages and applications of SAHs, their worldwide production and consumption continue to increase along the last decades. However, further applicability spread of SAHs is limited owning to the fact that their availability is usually restricted to petroleum-based synthetic polymers, which leads to high production cost and non-environmental friendly properties [13, 14].

Hence, the demand and interest for natural-based polymers have significantly increased from the viewpoint of their commercial and environmental advantages for SAHs [15]. Among natural polymers, polysaccharides constitute the main source of superabsorbent hydrogels, due to their unique properties, such as their biodegradability, nontoxicity, and renewability [4]. In fact, the first superabsorbent polymer was prepared from starch-grafted polyacrylonitrile, a combination of synthetic polymer and

polysaccharide, in the late 1960s [16]. Since then, many natural polymers, such as starch [17], cellulose [9], chitosan [18], guar gum [19], pectin [20], gelatin [21], etc., have been employed for preparing biodegradable and nontoxic SAHs. The presence of the polysaccharide ensures the biodegradability, biocompatibility, and nontoxicity of the SAHs. However, it is widely recognized that synthetic gels are much tougher and more resilient than gels found in nature [22]. This has led to an intense research in order to improve the toughness and stretchability of natural hydrogels [22] that has originated a wide range of possible combinations of polysaccharides and synthetic polymers. One of the best methods for the synthesis of biopolymer-based networks is free-radical graft copolymerization of vinylic monomers onto polysaccharide backbones leading to crosslinking their chains. In addition, modifying the chemistry of the polysaccharide before and after the crosslinking, as well as varying the degree of crosslinking, the swelling of hydrogels can be tailored to exhibit specific properties. Indeed, several factors can affect the swelling ratio and the mechanical properties of these networks, such as the fraction of ionizable groups along the polysaccharide backbone, the density of crosslinking, the conditions of synthesis (initiator concentration, temperature, etc.), and the presence of salt solutions.

Besides, polysaccharide-based SAHs can swell and contract in response to external stimuli such as heat, pH, electric field, or chemical environment. Among these, pH-sensitive polysaccharide-based SAHs have been extensively investigated for their potential use in site-specific delivery of drugs in the gastrointestinal tract [23] and for the removal of ionic pollutants in wastewater treatment [24].

Another alternative to improve polysaccharide-based SAHs toughness and reduce the final price of the product in the market is to form nanocomposites from hydrogels with clay minerals such as montmorillonite [25], attapulgite [26], kaolin [27], and bentonite [28] in high proportions. Much attention has been paid to this approach because, in addition to better mechanical properties, interaction of mineral powders with the reactive sites of natural polymers has demonstrated enhanced swelling ability, thermal stability, and release rate of fertilizers and active compounds [15].

Nowadays, the synthesis of SAHs with an ideal combination of water and salt absorbency and mechanical properties remains a challenge also for polysaccharide-based materials. As a consequence, an increasing research is now focusing on novel and optimized combinations of polysaccharides, synthetic monomers, and mineral clays, in which typically the effect of synthetic parameters is systematically studied for obtaining maximum absorbency in diverse aqueous solutions according to specific practical applications. This work aims to summarize a wide part of these combinations and describe the specific synthetic proposals and properties, as well as applications of the most reported polysaccharide-based macroscopic superabsorbing networks.

2 Synthesis

Polysaccharides are a wide range of natural biopolymers formed by repeating saccharide units linked by glycosidic bonds. Most polysaccharides are linear, although highly branching degrees are also common. All monosaccharide units

can be similar, this is the case of homopolysaccharides, or they can present different saccharide structures, leading to distinct physicochemical properties. Most polysaccharides in their original form are not able to produce stable hydrogels [6], which is essential for further applications both in agriculture and biomedical field. For this reason, heteropolymeric networks are preferentially prepared with polysaccharides, where two or more polymeric chains, natural, synthetic, or their combination, form a crosslinked network. Thus, polysaccharides need to be chemically or physically crosslinked in order to obtain SAHs. Networks obtained by covalent linkages (chemically crosslinked) remain more stable against variable external conditions than physically crosslinked hydrogels [29]. The main disadvantage of chemical crosslinking is the toxicity of residual vinylic crosslinkers, which can be a great concern for the synthesis of nontoxic SAHs [30]. In this sense, physical hydrogels would be preferred versus chemically crosslinked networks for biomedical and soil treatment applications. Besides, when physical interactions (such as physical entanglements, electrostatic interactions, van der Waals interactions, H bonding, or hydrophobic interactions) build up the three-dimensional networks of SAHs, crosslinkings are reversible, and this offers the unique characteristic of obtaining crosslinkings able to be modulated as environment conditions change [29, 30]. Thus, depending on the polysaccharide employed in SAH preparation, different crosslinking mechanisms take place. Furthermore, the type and concentration of active groups in the biopolymers, the effectiveness of the crosslinking interaction/reaction, the ionic strength (for charged networks) [31], the rigidity, and the hydrophilicity of the covalent crosslinking agent [32] are some of the factors that have to be taken into consideration when polysaccharide networks are formed in order to modulate the final swelling and mechanical properties of the gel.

The general synthesis pathway for SAHs starts with vinyl monomers containing hydrophilic side groups, ionic and/or ionizable groups which are copolymerized with other multifunctional vinyl monomers leading to covalently crosslinked copolymeric networks, as it is schematized in Fig. 1 for a hypothetical polysaccharide. In case of polysaccharide-based SAHs, this is also the most employed synthetic way for commercial production.

In the synthesis of polysaccharide-based SAHs, the starting materials are the polysaccharide chains, thus, more or less hydrophilic polymers that cannot be further polymerized, and, therefore, they must be crosslinked by means of their active functional groups with external molecules in order to obtain highly hydrophilic networks. Usually, these external molecules are synthetic vinylic monomers which polymerize in the presence of polysaccharide chains resulting in copolymeric networks [33] (Fig. 2). For simplifying, the most common monomers are those traditionally employed also in synthetic SAHs. This is the case of the anionic acrylic acid (AA) [14]; hydrophilic monomers like acrylamide (AAm) [34], methacrylamide (MeAm) [35], and vinyl pyrrolidone (VP) [30]; or monomers like acrylonitrile (AN) [36], for which postpolymerization modification reaction (hydrolysis) leads to highly hydrophilic systems (Table 1). Especially, acrylic acid and its derivatives are the main monomers used in the synthetic absorbent polymers, which present great water absorbency but have poor salt-tolerant capacity [37].

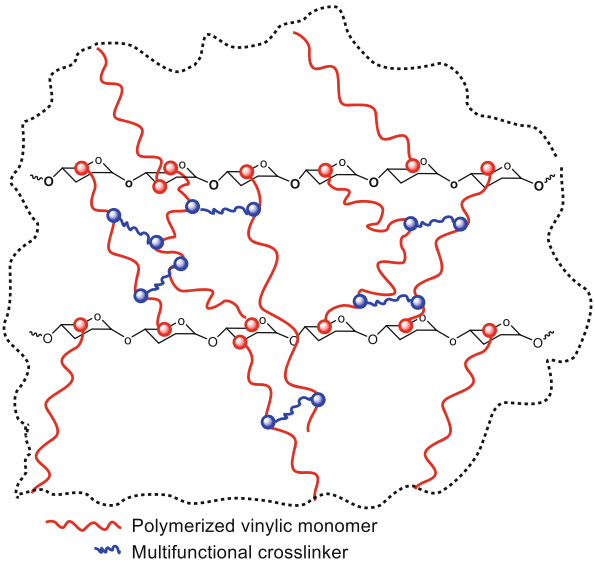

Fig. 1 Scheme of crosslinked network resulting from graft copolymerization of vinylic monomers and multifunctional crosslinkers onto polysaccharide backbone

Polymerization reactions of these monomers for grafting onto polysaccharide backbones are typically initiated at high temperatures (50–70 °C) by water-soluble redox initiators, such as potassium persulfate (KPS), sodium persulfate (NaPS), and ammonium persulfate (APS), especially when acrylic derivatives are used. Ammonium cerium(IV) nitrate (ACN) typically is employed when acrylonitrile takes part in the polymerization, and more recently, Pourjavadi et al. have included it for acrylic derivative grafting onto chitosan [36]. Nevertheless, some alternatives have been reported in order to develop crosslinking reactions at room temperature such as the redox system benzoyl peroxide (BPO) and 4-dimethylaminobenzyl alcohol (DMOH) [38], azobis(isobutylamine hydrochloride) (AIBA) radical initiator [33], or UV initiation [39]. Microwave-initiated synthesis has been also explored but did not exhibit significant improvement over the conventional techniques [40].

However, the most extended approach for chemical crosslinking includes an additional crosslinking step by multifunctional vinyl compounds, as is usual for synthetic SAHs. These multifunctional crosslinkers are typically glycidyl methacrylates, such as the divalent *N, N′*-methylenebis(acrylamide) (NMBA), widely used for acrylate polymerization. More recently, trimethylolpropane triacrylate (TMPTA) ester has been used as crosslinking agent based on its triple-double bond functionality, which has showed similar reactivity leading to highly crosslinked gels with high strength [27].

The general mechanism for grafting and crosslinking reaction can be explained as it is depicted in Fig. 2. Persulfate initiators generate by heating sulfate anion radicals which may strip down the hydrogen of –OH groups (additionally $–NH_2$ in polysaccharides like chitosan) of polysaccharide molecules forming macroradicals. These macroradicals react with vinylic monomers producing their chain propagation which leads to the grafting of synthetic polymers onto polysaccharides.

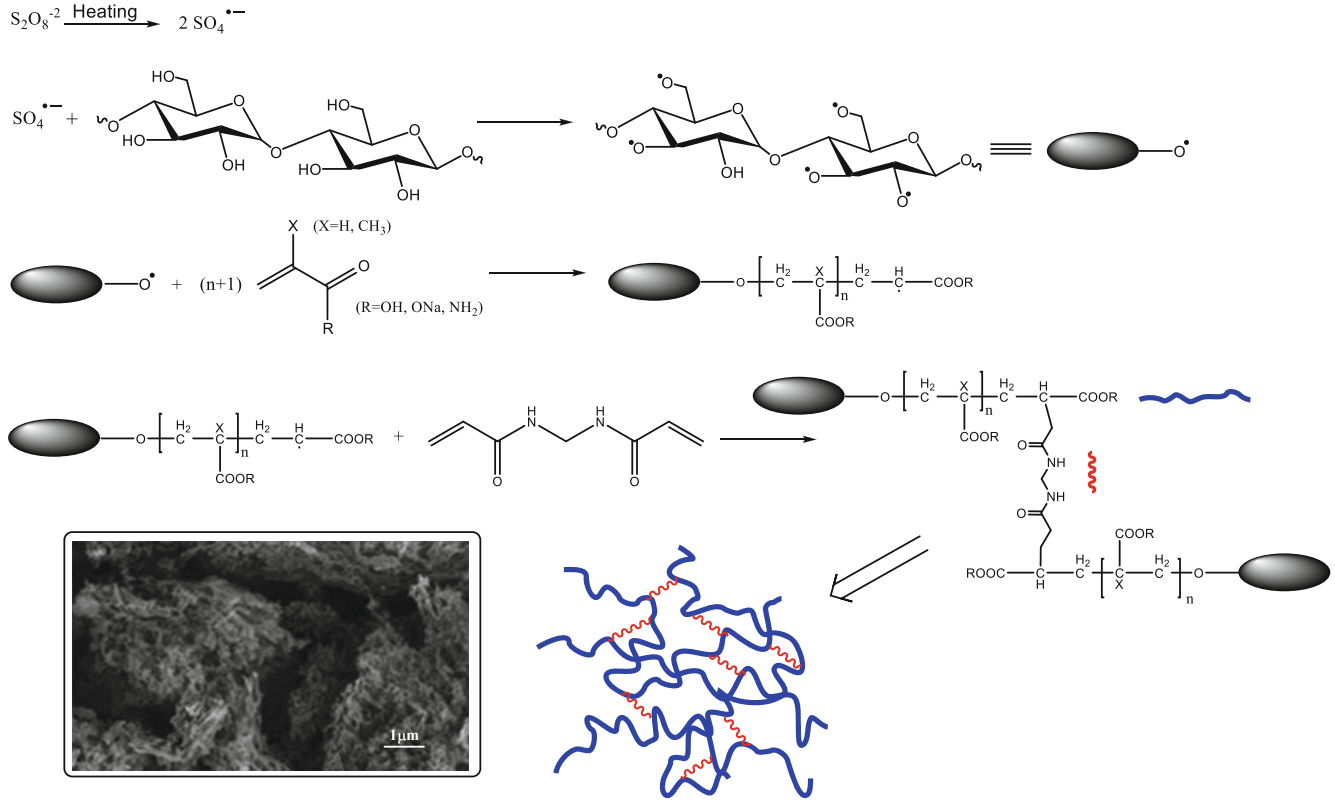

Fig. 2 Schematic representation of the general mechanism of free-radical copolymerization of polysaccharides with vinylic monomers (acrylic derivatives) in the presence of multifunctional vinylic crosslinking agents (NMBA)

Table 1 Different combinations of monomers for grafting, crosslinking agents, polymers for semi-IPN formation, added clays, and modifications used to prepare SAHs of some of the main polysaccharides

Types	Monomer/s	Initiator	Crosslinker	Polymer/clay/ modification	Ref.
Alginate	AAm	KPS	–	Agar-agar	[64]
	AAm/AA	APS	NMBA	Clinoptilolite	[65]
	MeAm	APS	NMBA	Hydrolysis	[49]
	AAm	KPS	NMBA	Kappa-carrageenan	[66]
	AA	APS	NMBA	PVP	[13]
	AA	APS	NMBA	Sodium humate	[7]
Chitosan	AA	APS	NMBA	PVP	[60]
	AA	APS	NMBA	Thiourea–formaldehyde resin–cellulose	[4]
	AAm	UV irradiation	NMBA	Hydrolysis	[39]
	AA/AAm	KPS	NMBA	Hydrolysis	[67] [4]
	AA/VPD	AIBA	NMBA	*N,O*-carboxymethyl chitosan	[4]
	AN	ACN	–	Hydrolysis	[31] [68]
Guar gum	AAm	KPS/MW irradiation	NMBA	Hydrolysis	[40]
	NaA/styrene	APS	NMBA	Attapulgite	[26]
	4-Dimethylaminopyridine (DMAP)	–	–	–	[42]
	NaA	APS	NMBA	Rectorite Attapulgite Sodium humate	[7, 19, 58]

	NaA/AAm	NaPS	–		[69]
Pectin	–	–	$CaCl_2$, ethylene glycol diglycidyl ether (EGE), glutaraldehyde	–	[20]
	AA/2-acrylamido-2-methylpropane sulfonic acid (AA, AMPS	APS	NMBA	Foaming agents	[5]
Starch	AAm)/ diallyldimethylammonium chloride (DMDAAC)	APS		Sodium starch sulfate Hydrolysis	[46]
	AA	APS	NMBA	Attapulgite	[43]
	AN	–	Dimethylformamide–sulfur trioxide (DMF–SO_3) complex	Sodium starch sulfate Hydrolysis	[44]
	KA/AAm	Ammonium persulfate-*co-N,N,N,_N_*-tetramethyl ethylene diamine (APSTMEDA)	Trimethylolpropane triacrylate ester	Inverse suspension polymerization	[27]
	AA	KPS	NMBA	Phosphate rock Starch/sulfonated corn starch	[8]
	AA/am	BPO/DMOH	NMBA	Corn starch/ethylene-*co*-vinyl alcohol thermoplastic Blend	[38]
	AA	APS	NMBA	Attapulgite Cellulose nanowhiskers	[17, 47]
	2-(Dimethylamino)ethyl methacrylate	Potassium permanganate/ sulfuric acid	–		[45]

Simultaneously, during chain propagation, crosslinker, NMBA, takes part in the free-radical polymerization reaction resulting in randomly and heterogeneously crosslinked structures.

Most of commercially available SAHs are crosslinked by polyacrylates with extremely high molecular weight and no biodegradability, which may result in environmental pollution, due to the fact that their major applications are related to disposable goods. For this reason, the substitution of conventional synthetic polymers as crosslinking agents for polysaccharides is an interesting approach to obtain entirely biodegradable SAHs. In this sense, SAHs of guar gum and starch have been obtained without any crosslinking procedure, by esterification of starch [41] and guar gum [42] with succinic anhydride when 4-dimethylaminopyridine (DMAP) was employed as esterification promoter (Fig. 3).

Regarding polysaccharides, the most employed for SAH preparation are starch and heteropolysaccharides, such as chitosan, alginate, pectin, and guar gum. Starch is a renewable and natural polymer produced by most plants and could be found in large amounts in basic foods of human diets such as wheat, potato, corn, and rice. Starch has been widely studied for many decades due to its low cost, biodegradability, and versatility. This polysaccharide is made of α-D-glucose units, bonded to each other through α(1 → 4) glycosidic bonds. Pure starch contains a mixture of linear and branched polymers that corresponds to amylase (20–25%) and amylopectin (75–80%), respectively [41]. Starch contains a large number of –OH groups in their structure (Fig. 4). These hydrophilic groups make it one of the best raw materials for superabsorbency. Besides, starch backbone can be grafted by different monomers to vary its hydrophilicity or add polyelectrolyte nature depending on the reagent and conditions used. For instance, grafting of acrylamide [43], acrylonitrile [44], 2-(dimethylamino)ethyl methacrylate [45], and acrylic acid [43, 46] onto starch has been reported (Table 1), and hydrogels with high thermal stability, biodegradability, and good water absorption capacity have been typically obtained [47]. Chemical modification of starch prior to the grafting via oxidation, hydrolysis, esterification, and etherification, among others, has been also studied, spreading the synthetic versatility of this biopolymer [43].

Alginate is a linear anionic polysaccharides of (1 → 4)-linked α-L-guluronate (G units) and β-D-mannuronic acid (M units) residues, which vary in amount and sequential distribution along the polymer chain depending basically on the seaweed species [48] (Fig. 5). Alginates are traditionally used in food industry as thickener and suspension-stabilizing agent owning to its useful ability to form gels by simple "ionic crosslinking" reaction with calcium cations. Divalent cations form ionic bridges between alginate chains that have been explained by the so-called egg-box model (Fig. 4). However, ionic crosslinking of alginate can lead to high crosslinking density and low absorptions [29]. Due to this, chemical crosslinking has been also explored as synthesis via for alginate-based SAHs [49].

Chitosan is an aminopolysaccharide obtained by the deacetylation of natural chitin which is the second most abundant biomacromolecule in the world. Chitosan is a copolymer of β-(1–4)-linked 2-amino-2-deoxy-D-glucopyranose (deacetylated unit) and β-(1–4)-2-acetamido-2-deoxy-D-glucopyranose (acetylated unit) [50].

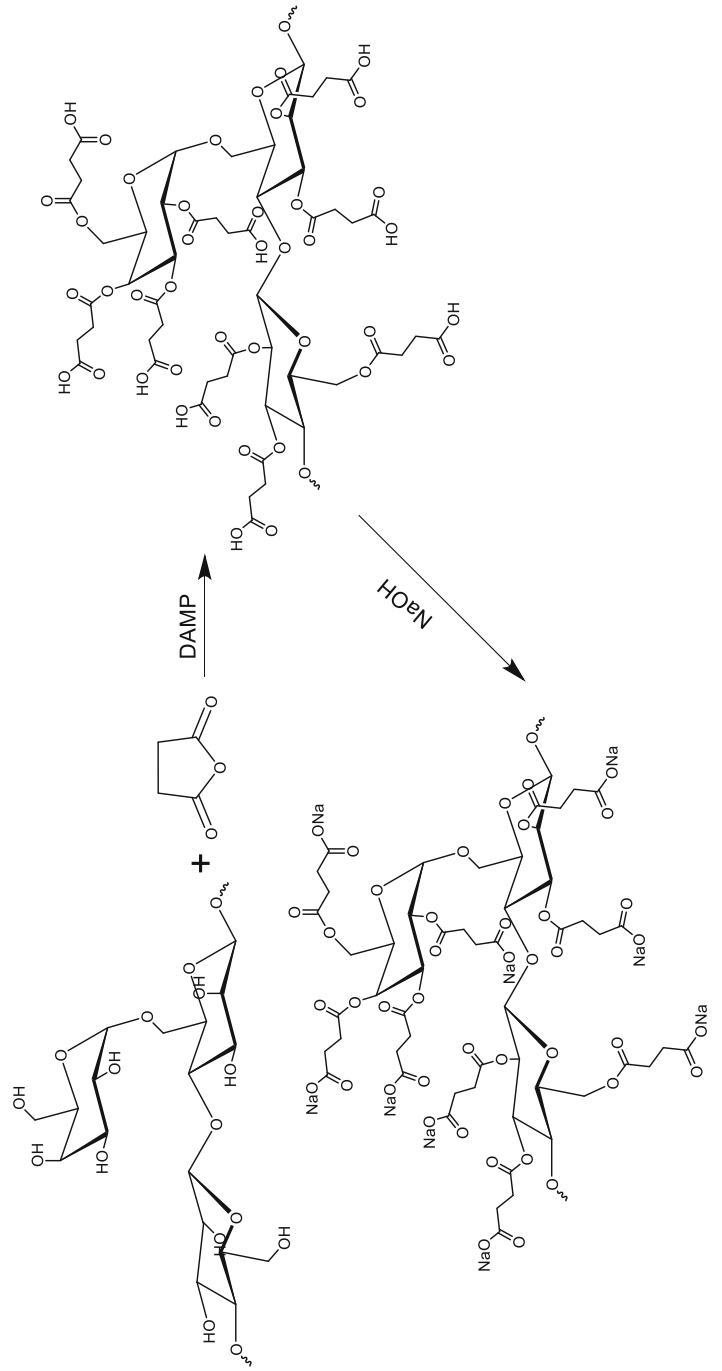

Fig. 3 Guar gum crosslinking by succinic anhydride in the presence of 4-dimethylaminopyridine

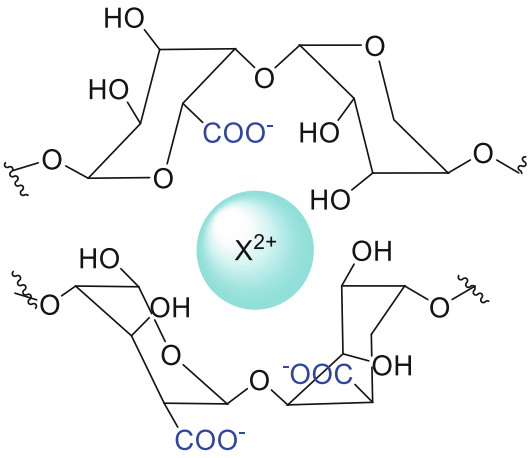

Fig. 4 Schematic representation of ionic crosslinking of alginate in the presence of divalent cations

This biopolymer has both reactive hydroxyl and amino groups which can be used to easily chemically modify its chemical structure, and properties, under mild reaction conditions. Like other natural polysaccharides, chitosan has attractive biocompatibility, biodegradability, and nontoxicity. However, it has demonstrated additional properties such as immunostimulating properties, suppressing tumor growth, or promoting resistance to infections by microorganisms that have made exponentially to increase the worldwide interest on this biopolymer to be applied as drug carrier, biomedical material, and absorbent in water treatment [51, 52]. Chitosan does not display consistent gel-forming ability at low pH, where protonation of amine moiety takes place. Nevertheless an efficient approach to improve the mechanical properties of these gels is also the graft polymerization of vinylic monomers such as acrylic acid, acrylamide, acrylonitrile, or vinyl pyrrolidone (Table 1). On another hand, chitosan is a weak base, and, consequently, cationic charges are accumulated along its backbone at low pH values. This leads to electrostatic repulsions, and as a consequence, chitosan-based SAHs display a contrary pH sensitivity of typical pH-sensitive acrylic derivatives that lets them increase their swelling at acidic pHs and has made them the subject of numerous studies [53]. The proportion of accumulated cationic charges along chitosan backbone varies according to the external pH and the deacetylation degree of each chitosan, a consequence of its obtaining process from chitin [54]. The deacetylation degree is the parameter that indicates the molar percentage of monomeric units that have amino groups and varies from 0 (chitin) to 100 (fully deacetylated chitin).

Pectin is a complex mixture of polysaccharides that makes up about one third of the cell wall dry substance of higher plants. It is a naturally occurring biopolymer employed for many years in food industry as colloidal stabilizer and gelling agent [55]. Pectin is abundantly found in citric fruits, mainly in lemon. In fact, commercial pectin is extracted from citrus peel and apple pomace, by-products of juice manufacturing. Its composition varies with the source and the conditions applied during isolation, storage, and processing of plant material. Thus, although pectin has

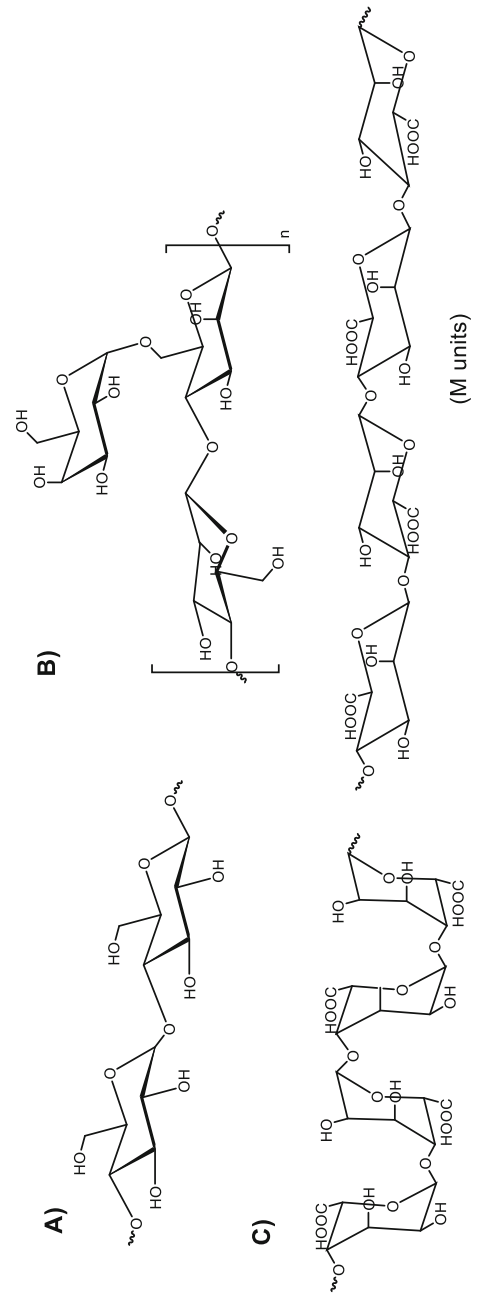

Fig. 5 Chemical structure of main polysaccharides employed for SAH synthesis: (**a**) starch (amylose); (**b**) guar gum; (**c**) alginate, G and M units; (**d**) pectin; and (**e**) chitosan

been employed for centuries, its composition and structure are still not entirely understood [56]. At present, pectin is thought to consist mainly of D-galacturonic acid (GalA) units linked by α-(1–4) glycosidic linkages. These D-galacturonic acids have carboxyl groups that make pectin an ideal candidate to substitute synthetic acrylic acid polymers, without environmental problems. Its structure at adequate pH can present high amounts of ionic groups derived from the ionization of carboxylate moieties, resulting in an excellent polymer matrix for SAH preparation by ionic crosslinking [20]. In nature, most of carboxyl groups of galacturonic acid are esterified. The ratio of esterified to non-esterified galacturonic acid, or esterification degree (DE), will determine the properties and the kind of network formed in SAH preparation. In general, pectin classes based on the DE are high methoxyl (HM) pectins (DE ~60–75%) and low methoxyl (LM) pectins (DE ~20–40%) [56]. The non-esterified galacturonic acid units can be either free acids (carboxyl groups) or salts with sodium, potassium, or calcium. Some of the esterified units are naturally present as methyl esters and others, which are commercially treated with ammonia, as carboxamide groups (Fig. 5). According to DE, pectin-based SAH synthesis mechanism can be chemical or physical. In HM pectins the origin of SAH network consists of hydrogen bonds and hydrophobic interactions which bind the individual pectin chains together forming a 3-dimensional molecular net that results in a macromolecular gel [56]. The gelling mechanism is called a low-water-activity gel or sugar–acid–pectin gel. However, in LM pectins, ionic bridges are formed between divalent cations, usually calcium, and the carboxylate groups of galacturonic acid. In this case the gelling mechanism corresponds also to the "egg-box model." Consequently, LM pectins show calcium concentration and pH dependence to form gels [57]. In addition, the combination of hydrophilic acrylic polymers with biodegradable pectin leads to interesting hydrogels with potential applications as biomaterials exhibiting different properties depending on the composition and on the type of interactions within the network, attending to chemical crosslinking and hydrogen-bonding interactions [55].

Guar gum is a nonionic galactomannan polysaccharide extracted from the seed endosperm of the plant *Cyamopsis tetragonolobus* that has also been easily crosslinked by grafting vinyl monomers onto its backbone obtaining guar gum-based hydrogels with improved structure and high water absorption [26, 40]. However, no intensive information related to the application of this polysaccharide in superabsorbent fields has been reported [19, 58].

Regarding physical crosslinking, the simplicity of the synthetic procedures for SAH preparation that are based on the mixture of a solution of polysaccharide and a gelating medium is noteworthy. This is the case of polyelectrolyte polysaccharides, such as alginates, pectins, or chitosans, which present ionizable groups that at an adequate pH become charges that promote gelation in the presence of multivalent metal cations, typically Ca^{2+} or polyanions.

Therefore, SAHs of polysaccharides are mainly copolymeric hydrogels in which covalently bonded blocks of synthetic polymers are inserted as grafts or polyelectrolytes with ionic crosslinking in the presence of ions. But, in addition, more complicated combinations of physical and chemical crosslinkings have been investigated in the last years, resulting in different interpenetrating polymer network (IPN)

and semi-IPN structures [21, 39]. As it is well known, heteropolymeric network can be also prepared by combination of different polysaccharides and synthetic polymers in the crosslinked structure of the SAHs. If all implied polymers are crosslinked, the obtained network is the so-called full-interpolymer network (IPN or full-IPN). However, if only some types of polymers are crosslinked and one or more polymers remain uncrosslinked, the obtained network is referred as semi-IPN [59]. Despite the high yields of crosslinking reactions, a mixture of crosslinked and uncrosslinked polysaccharides is usually formed in SAH preparation, especially when low crosslinker concentrations are used. Thus, strictly speaking, most hydrogel networks prepared from polysaccharides would correspond to semi-IPN structures (Fig. 6). Nevertheless, typically semi-IPN term would be employed to refer to SAH networks in which a covalently crosslinked polysaccharide is combined with hydrophilic polymers which as a consequence of strong physical interactions, usually hydrogen bonding, are distributed throughout the network. The most employed polymers for semi-IPN superabsorbent hydrogel preparation of polysaccharides are poly(vinyl alcohol) (PVA), [60] and poly(vinylpyrrolidone) (PVP) [13]. The content of these polymers in semi-IPNs has demonstrated not only to increase the water absorbency, and swelling rate, but also to control and improve greatly the surface morphology of the hydrogels. So, Liu et al. [60] synthesized chitosan-*graft*-polyacrylic acid/polyvinyl alcohol semi-IPNs and observed that looser and best-defined porous structures were obtained, contrasting to chitosan-*graft*-polyacrylic acid hydrogels. In addition, pH stability of chitosan-*graft*-polyacrylic acid/polyvinyl alcohol semi-IPNs was higher when PVA was incorporated in chitosan-*graft*-polyacrylic networks. However, Wang et al. [13] found in alginate-*graft*-poly(sodium acrylate)/PVP semi-IPNs

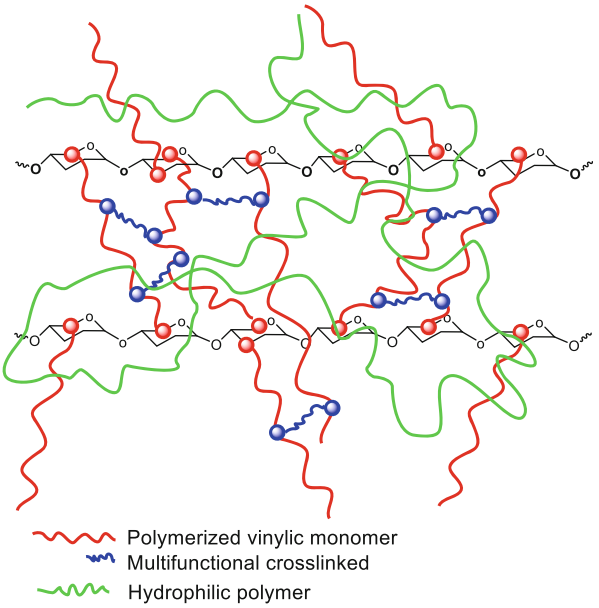

Fig. 6 Schematic representation of a semi-IPN polysaccharide-based network

that the incorporation of moderate amount of PVP was favorable to enhance the swelling rate but the excessive addition of PVP made it to decrease.

As it has been previously mentioned, polysaccharides are usually modified in order to increase their water absorbency and reduce salt effect. To this, introducing hydrophilic groups that have a greater tendency than commonly employed carboxylic acid groups to ionize is a well-known strategy. Starch sulfate is the most known example of modified polysaccharide to obtain enhanced SAHs. The introduction of sulfate groups into starch makes the starch soluble at room temperature and more salt tolerant. Since sulfate groups ionize more readily than typically used carboxylic acid groups, the degree of association with the mobile ions of solutions is lower than that of carboxylic acid groups [38]. As a consequence, the effect of ionic strength on the swelling of the network is not so significant, and saline absorbency of the hydrogel is greatly improved. Peng et al. [46] grafted acrylamide and diallyldimethylammonium chloride into sulfate-modified starch backbone by solution polymerization, and a reinforced salt tolerance of the resulting superabsorbent hydrogel was shown. It can be observed that the introduction of sulfate groups produces an additional crosslinking factor, which can be exploited to reduce the dose of chemical crosslinker. At the same time, this modification produced an amphoteric hydrogel in which swelling of the network was not affected by pH of the absorbed solution. Some disadvantages have been also encountered for starch sulfate synthesis, such as the degree of substitution that cannot be easily controlled and degradation of starch chain that may occur [38, 44]. Thus, several different methods have been suggested for synthesizing starch sulfate: tertiary amine–SO_3 complex, dimethyl sulfoxide (DMSO)–SO_3 complex, chlorosulfonic acid in organic solvent, and sulfuric acid [61].

Another synthetic approach to increase water absorptions of hydrogels is hydrolysis reaction. This reaction is commonly carried out on the final crosslinked structure [43], being specially usual for hydrogels that contain graft-polymerized acrylonitrile [44, 55]. Nevertheless, the hydrolysis of polyacrylic derivatives has been also widely explored. For instance, superabsorbing hydrogels have been prepared through alkaline hydrolysis of alginate-*graft*-polymethacrylamide [13] or guar gum-*graft*-polyacrylamide networks [40].

Hence, post-synthetic hydrolysis is usually the key route that confers superabsorbent properties to basic hydrogels. For example, Guilherme et al. [62], after chemical modification of cashew gum by the incorporation of glycidyl methacrylate (GMA) and copolymerization with acrylic acid, obtained hydrogels at 40 °C (3–4.5 h). As a consequence of the hydrolysis, water uptake increased up to 1500 times, and hydrogels could be classified as water superabsorbent materials.

Pore formers have been also included in polysaccharide SAH preparation in order to improve surface morphology, and its effect on water absorbency and swelling velocity has been analyzed. This is the case of surfactant self-assembling templating pore-forming technique. This technique is based on the fact that surfactant can self-assemble forming micelles in aqueous solutions. Micelles act as templates in the polymerization reaction process to produce more micropores within network structure [26]. Porous alginate hydrogels with controlled pore size were successfully developed by varying the surfactant concentration [24]. This technique was also

employed when guar gum-*g*-poly(sodium acrylate-*co*-styrene)/attapulgite (GG-*g*-P (NaA-*co*-St)/APT) superabsorbent hydrogels were prepared by simultaneous free-radical graft copolymerization reaction of guar gum (GG), partially neutralized sodium acrylate, styrene, and attapulgite using *N,N′*-methylenebisacrylamide as crosslinker and ammonium persulfate as initiator in aqueous solution and in the presence of nonionic and cationic surfactants [26]. This study indicated that the incorporation of proper amounts of neutral surfactants in the preparation process of hydrogel gives rise to the improvement of the initial swelling rate through the creation of additional porosity in the hydrogel network, while for cationic surfactant, the attractive forces between anionic polymeric chains and cationic surfactant molecules lead to the physical crosslinking in the hydrogel networks reducing the network free space and slowing the diffusion of water molecules into the hydrogel.

$NaHCO_3$ has been also employed as a foaming agent during the simultaneous grafting and crosslinked of pectin with, NMBA, and as ionic monomers, acrylic acid and 2-acrylamido-2-methylpropane sulfonic acid, resulting in superporous hydrogels [5].

Inverse suspension polymerization has been also employed for graft copolymerization on polysaccharides for SAH preparation as an alternative to solution polymerization [63]. This synthetic method leads to hydrogel preparation in homogeneous granular form and allows higher monomer contents. Due to this, inverse suspension polymerization method affects both the properties of the polymer, such as particle size and toughness, and the economics of the process. Superabsorbent starch-*graft*-poly(potassium acrylate-*co*-acrylamide) was synthetized by inverse suspension polymerization formed by cyclohexane and the surfactant mixture of Span 60 and Span 20, resulting in fine particles of 1.5 mm of SAHs [27].

3 Properties of Polysaccharide-Based Superabsorbents

3.1 Swelling Properties

The ability of the SAHs to absorb and retain water or aqueous solutions is crucial for their applications. Structures of superabsorbent hydrogels are insoluble, and their properties depend on the monomers used and the crosslinking density, being the swelling capability closely related to them. Several different parameters have been employed to study the swelling capability of these materials, being the most used ones described below.

The equilibrium water absorption (Q_{eq}) of the SAHs, also known as swelling degree (SD) or swelling ratio (SR), can be calculated using the following equation:

$$Q_{eq} = \frac{m_2 - m_1}{m_1} \tag{1}$$

where m_2 and m_1 are the weights of the swollen gel and the dried sample, respectively.

Water retention (WR) is defined as:

$$WR = \frac{W - W_d}{W_0 - W_d} \, x \, 100 \tag{2}$$

where W_0 is the weight of the completely swollen sample, W_d is the weight of the dry sample, and W is the weight of the sample heated for different times at certain temperature [13, 17, 70].

It is important to notice that superabsorbent hydrogels not only have high swelling degree; they also have excellent water retention capacity. That is, they can imbibe a large amount of aqueous solution and release it slower than traditional absorbent hydrogels under the same conditions.

3.1.1 Swelling Kinetics

Swelling capability could be considered one of the most important factors to evaluate the performance of the designed superabsorbent hydrogels. However, the swelling rate is also an important index for SAHs limiting some of their applications. When the evaluated polysaccharide-based hydrogels have included synthetic comonomers or other agents (nanoparticles, clay, etc.) in their network, the kinetic studies could give a valuable information about the influence of these segments on the swelling [31, 66, 71]. The swelling rate depends on the swelling ratio, surface area, particle size, and polymer density. The Schott's pseudo-second-order kinetics model is commonly used for swelling rate evaluation defined as:

$$\frac{t}{Q_t} = \frac{1}{K_{is}} + \left(\frac{1}{Q_\infty}\right) t \tag{3}$$

where Q_t is the swelling ratio at time t, Q_∞ is the theoretical equilibrium swelling ratio, and K_{is} is the initial swelling rate constant. The values of K_{is} and Q_∞ could be determined by the experimental fitting from the slope and the interception of straight line obtained from the plot of Eq. (3).

3.1.2 pH Sensitivity

pH sensitivity has especial relevance for SAHs used as materials with self-healing and self-sealing crack capability in mortars [72, 73] and for controlled releasing of nutrients and drugs [8, 40, 69, 74]. The swelling capability of these hydrogels varies with the pH, and the change of the water absorption at different pH indicates the excellent pH sensitivity of these compounds. pH-sensitive groups of the SAH matrix (i.e., sulfonic acid, carboxylic acids, or amines) can interact with each other at specific pH changing the swelling capability. The acidity and basicity of the environment conditions change the charge of the polar groups of the hydrogels, and when identical charges are formed, they repel one another, creating free volume in the network and increasing the water absorbed by the hydrogel and its swelling capability. This effect depends on the nature of SAHs, those hydrogels containing anionic polymer such as polysaccharides (carboxymethyl cellulose or chitosan, etc.)

or common synthetic polyacids present in SAHs (poly(metha)acrylic acid, poly (sodium acrylates), and poly(styrene sulfonate)), with COO^- or COOH groups presenting pH sensitivity. Under acidic medium, pH < pKa, (depending on pKa of the polymer, around 2–4 for the most used polymers in SAHs), the –COOH or $–SO_3H$ groups remain protonated, the hydrogen-bonding interaction among these groups is strengthened, and physical crosslinking between the macromolecular chains of the matrix is generated, restraining the expansion of the hydrogel network. The swelling capacity of the SAHs with acid groups is lower than in water due to equilibrium swelling that will occur at shorter diffusion times. As the pH increases, pH > pKa, the disruption of the hydrogen bonds occurs; the dissociation of the acid groups induces the reinforcement of anion-anion repulsions increasing the swelling of the materials. In basic media, the concentration of anionic groups ($–COO^-$ or $–SO_3^-$) increases, and electrostatic repulsion causes chain expansion as well as macroscopic expansion. Under highly basic media (pH > 9–10), some authors have described a swelling loss related to the charge screening effects of the counterions (Na^+); the swelling ratio of the hydrogels could decrease owning to a non-perfect anion–anion repulsion [75–77].

The pH effect could be more complex in hydrogels with acid and basic moieties, such as quaternary ammonium-*graft*-poly(acrylic acid-*co*-acrylamide) hydrogels [4]. The water absorbance maximum of this hydrogel is located at pH 7. In this case, at pH 2 the swelling is very poor, the –COOH groups form hydrogen bonds, and the repulsive force of the anions is weakened. Also, at pH ≤ 3, the quaternary ammonium is positively charged, $-N^+(CH_3)_3$, and is shielded by counterions (Cl^-) through the screening effect, preventing the repulsion effect. At pH > 8, the carboxylic groups are deprotonated, decreasing the hydrogen bonds present in the system. However, the presence of Na^+ and OH^- ions in the media reduces the swelling ratio due to the charge screening of the Na^+ in the buffer. As a result, this kind of hydrogels has double pH sensitivity, at acid and basic conditions.

Finally, it is important for some applications to evaluate the reversibility of the pH response of the materials by several cycles in which swelling–deswelling capability is tested in two buffer solutions of pH 7 and 2, respectively. When the hydrogels present acid moieties, they usually switches between On (highly swollen, pH 7) and Off (not swollen, pH 2) states [71, 75].

3.1.3 Effect of Salt Solutions in Water Absorption on SAHs

The osmotic pressure can be considered as the main driving force for SAH swelling, and it is proportional to the ion concentration in the medium. Also, it is to be noticed that the swelling properties in saline solution are especially significant to the practical application of this kind of hydrogels. The influence of the ions (cations and anions) on the swelling capability of the SAHs can be analyzed by different salt solutions. Usually, the study of the salt effect on the swelling capability of the hydrogels is carried out by using different salts and concentrations, such as NaCl, $MgCl_2$, $CaCl_2$, or $AlCl_3$, among others. One of the most common studies evaluates the influence of monovalent (NaCl), divalent ($CaCl_2$), and trivalent ions ($AlCl_3$) at

0.5 M and 25 °C on the hydrogel swelling. The measurement could be compared by using a dimensionless salt sensitivity factor, *f*, defined as:

$$f = 1 - \frac{W_{\text{saline}}}{W_{\text{water}}} \tag{4}$$

where W_{saline} and W_{water} are the swelling capacity in saline solution and in water, respectively [31, 47, 77]. Swelling ratio for superabsorbent hydrogels depends on the ions present in the medium, cations radius, and charge, being sensitive factors that could change the swelling capability of the materials drastically. The f values indicate the saline effects, so when its value is close to 0, the ionic effect in the swelling of the saline solution is low, but when f is close to 1, the saline effect is strong.

The cation size influences the swelling degree of the SAHs. As an example, some authors have analyzed the influence of the radius in monovalent cations in kappa-carrageenan, a polysaccharide with SO_3^- group. They have suggested that this polysaccharide could form intermolecular cation bridges between the sulfate groups with large cations such as K^+, Rb^+, and Cs^+; however, these interactions are not present with small cations (Li^+ and Na^+). That is, the swelling capacity of carrageenan is higher in LiCl and NaCl solutions than in KCl, due to its affinity for crosslinking with K^+. Nonetheless, the influence of valence on the water absorption is not so relevant for SO_3^--substituted hydrogels [75, 78]. The swelling capacity of hydrogels with carboxylic moieties varies significantly in mono-, di-, and trivalent cation solutions. Multivalent cations, such as Ca^{2+} and Al^{3+}, form coordination complexes with carboxylate groups, and these interactions act as additional crosslinking and reduce dramatically the water absorption capability [13, 71, 77].

3.1.4 Controlled Load/Release of Solutes

Some applications of these materials, such as controlled release of drugs, fertilizers, or nutrients, are based in the capability of the hydrogels for loading and releasing those substances. Polysaccharide-based SAHs are of especial relevance for this kind of applications due to their excellent biocompatibility, nontoxicity, and biodegradation that make them eco-friendly materials ideal for being used in agriculture. The capability of loading a solute by a hydrogel as a function of time could be calculated by Eq. (5):

$$\text{Loading} = \frac{S_0 - S_t}{S_t}\ x\ 100 \tag{5}$$

where S_0 is the initial concentration of solute in the supernatant prior to the contact with the hydrogel and S_t is the residual concentration of the solute in the supernatant after a time *t*. On the other hand, the solute release percentage could be defined as:

$$\text{Release} = \frac{R_t}{L}\ x\ 100 \tag{6}$$

where *L* is the initial solute concentration loaded in the hydrogel and R_t is the cumulative amount of solute released at time *t*.

Several SAHs with good loading/releasing capability have been already developed. A controlled release of soil nutrients was obtained from chitosan–cellulose hybrid grafted by acrylic acid capable to deliver fertilizers, for this systems a slow nutrient release systems in soil have been fabricated with a final release around 90% [18]. The low rate on the releasing process is highly interesting in agriculture, mainly as soil conditioner or nutrient carrier is long lasting. Also, successful drug delivery systems have been obtained by using alginate and starch-based superabsorbent hydrogels achieving a maximum release of 70–100% at pH 7 [23, 79].

3.2 Mechanical and Thermal Properties

Polysaccharide-based hydrogels despite of their unique properties such as biocompatibility, biodegradability, and nontoxicity present poor mechanical strength. These materials present intrinsic structural heterogeneity and have no efficient energy-dissipation mechanisms. Usually dynamic mechanical analysis (DMA) is employed to study the mechanical and thermal properties of the hydrogels, in which an oscillating stress is applied in the material sample and the resultant strain is measured. The measurement strain is studied as a function of oscillatory frequency and temperature. DMA allows the characterization of the thermo- rheological properties of the SAHs [80, 81]. Commonly, they have poor toughness, low mechanical strength, and limited extension/recovery capability. Sometimes the lack of good mechanical properties could reduce the application ratio of SAHs, so it is a critical factor to improve. Several approaches have successfully been carried out in order to improve both thermal and mechanical properties of the materials such as incorporation of crosslinkers, double-network systems [82, 83], tri- or diblock copolymers [84], or nanocomposites [58, 75, 85–87], among others.

The thermal properties of these materials can be characterized by differential scanning calorimetry (DSC). Usually, DSC measurement in these materials assumes that only free water could be frozen, that is, the endothermic peak observed in the thermogram in a swollen and frozen sample corresponds to the free water melting present in the sample, being quantifiable by this method the free water amount in the hydrogels [88]. The difference between the DSC (free water) and the total water of the hydrogel measured by thermogravimetric (TGA) methods enables the calculation of the bound water present in the material [89–94].

3.3 Biodegradability

The increase of environmental problems often associated to synthetic polymers promotes the use of polysaccharide-based materials, being these good candidates for biodegradable SAHs [95]. Biodegradability of polysaccharide-based hydrogels is often required for applications in agriculture and biomedicine. Usually, the glycosidic linkages in the polysaccharide chains are degradable by microorganisms and hydrolytic enzymes, glycosidases. Some of the most common enzymes

used are α-amylase, that hydrolyzes (1 → 4) linkages between D-glucopyranosyl residues within the polysaccharide chain, and chitinase that is capable to hydrolyze chitin with a similar degradation process [95, 96]. For example, starch is converted to maltose and D-glucose by enzymatic degradation by amylase. Due to this, starch-based SAHs could be completely degraded. During their enzymatic degradation process, the enzyme caused swelling ratio variation.

SAHs based on polysaccharide could potentially be used as sanitary napkins, disposal dippers, and delivery systems for drugs or nutrients. After being used these materials could frequently end as a part of water residues and being treated as sewage. In this case, their biodegradability by using activated sludge is crucial. Yoshimura et al. had successfully tested the biodegradation of hydrogels by using activated sludge in several polysaccharide-based hydrogels containing succinic anhydride [41, 42, 97].

3.4 Antibacterial Activity

Superabsorbent hydrogels with applications in biomedicine, especially those designed to be used for wound healing [98], present a great biocompatibility, and some of them also have antibacterial properties [99]. Some polysaccharides such as chitosan and its derivatives present good bactericide properties. Chitosan has a well-known antibacterial activity, so the hydrogels based on this polysaccharide could be nontoxic, biodegradable, biocompatible, and have antibacterial properties [86, 100]. Chitosan derivatives such as quaternary ammonium chitosan also have good antibacterial properties and improve the poor water solubility of the original chitosan [101, 102]. Other possible approach developed in SAHs for biomedical uses without an intrinsic antibacterial activity is the incorporation of nanoparticles or bactericides in the hydrogel matrix. Some hydrogel composites have been developed in order to achieve these characteristics, for example, by adding silver or zinc oxide nanoparticles [103, 104]. Also, hydrogels loaded with gentamicin have been tested with good results [105].

4 Applications of SAHs

Similar to synthetic superabsorbent hydrogels, polysaccharide-based hydrogels have been employed for a wide variety of applications. However, the massive production of these materials is not available yet, so their applicability is estimated to increase markedly in the following decades. Until now, polysaccharide-based SAHs have been employed in areas as diverse as water treatment, biomedicine, agriculture, and building.

4.1 Water Treatment

According to the World Health Organization (WHO), nearly 12.6 million deaths each year are linked to unhealthy environments, being water pollution one of the

most serious environmental issues that our society faces, causing approximately 14,000 deaths per day [106], especially in developing countries. Currently employed materials for water purification purposes present low adsorption capacity and are nonbiodegradable [107]; it is therefore essential to obtain low-cost and effective adsorbents to remove pollutants from water. In this framework, the characteristic swelling of hydrogels when immersed in aqueous solutions may allow the penetration of pollutants and their subsequent interaction/binding with the specific functional groups, allowing very fast adsorption processes [74, 108].

4.1.1 Removal of Heavy Metals

It has been widely reported that the exposure to heavy metals such as cadmium, arsenic, lead, or mercury represents serious threats to human health. The removal of these heavy metals from water could be accomplished by crosslinked chitosan-based hydrogels. Wang et al. showed that Hg^{2+} ions could be adsorbed using chitosan-*graft*-poly(acrylic acid) hydrogels reinforced with attapulgite via the interaction of Hg^{2+} ions with –COOH, $–NH_2$, and –OH groups of the hydrogel [109].

Similarly, chitosan-*graft*-poly(acrylic acid) composite hydrogels have been employed for the removal of Cu^{2+} and Cd^{2+} ions [110, 111]. It is observed that the introduction of attapulgite yields porous surfaces which enhance water adsorption and allow such high swelling degrees. Kinetic experiments reveal that the 90% of the Cd^{2+} adsorption takes place during the initial 3 min (adsorption equilibrium is reached in 10 min). Overall, the high adsorption capacities and average desorption efficiencies obtained during the five consecutive adsorption–desorption processes suggest the potential reusability of these hydrogels.

Other polysaccharides, such as alginate, have been used for metal absorption applications in addition to dye removal. Recently, Agnihotri et al. have developed poly(acrylic acid/sodium alginate/sodium humate) SAHs capable of absorbing metal ions (Cu^{2+}, Pb^{2+}, and Fe^{3+}) and dyes (methylene blue and crystal violet) [112].

4.1.2 Photocatalysts for Dye Removal

Over the years many efforts have been directed toward the development of photocatalytic materials for the oxidation of organic compounds. Among the materials used for water purification and wastewater treatment, nanosized titanium dioxide (TiO_2) emerges as one of the most studied ones owing to its availability, low cost, high photostability, and chemical inertness [113, 114], although its successful application often depends on its associated toxicity and its recovery once it has been used. To avoid these issues, Gjipalaj et al. [24] developed through a cheap and eco-friendly approach millimeter-sized porous beads by alginate-based ionotropic gelation of commercial TiO_2-anatase powders. Alginate acts as a nontoxic, biocompatible, pore-directing template and binder, and the efficiency of such materials for the removal of different organic dyes from water was evaluated using both anionic (methyl orange) and cationic (methylene blue) dyes as a model of organic pollutants. It is observed that the methylene blue adsorption of the mesoporous microbeads having a BET surface area of 93 m^2/g is dramatically increased up to 55% in regard to 6.5% for the TiO_2 nanopowder samples even at concentrations as high as 1×10^{-4} M.

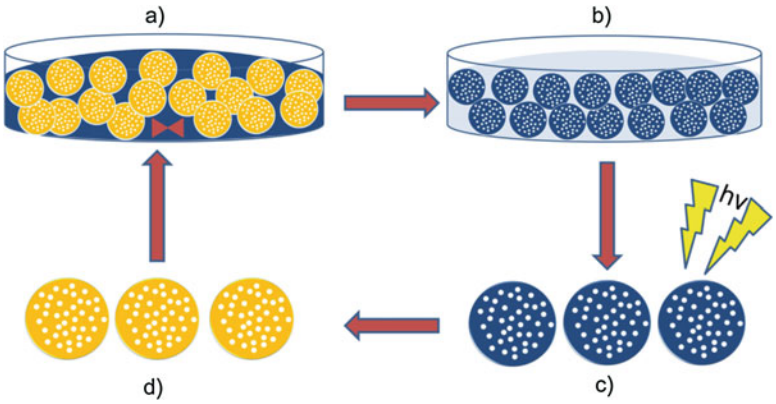

Fig. 7 Scheme showing the application of alginate–TiO_2 microbeads as pollutant scavengers. **(a)** The beads are dispersed in the solution by continuous stirring; **(b)** when mechanical stirring is stopped, the beads undergo rapid sedimentation; **(c)** the adsorbed dye is extracted via ozone–UV cleaning; **(d)** the beads can be reused for another adsorption/removal cycle. (Reproduced with permission from Ref. [24], Copyright (2017), Elsevier)

More interestingly, as depicted in the scheme of Fig. 7, once they have been used as photocatalytic absorbers, they undergo a rapid sedimentation, allowing their extraction and removal by ozone–UV cleaning (adsorbed dye is completely extracted from the beads). Thanks to their simple preparation, high adsorption, and reusability for another adsorption/removal cycle, these alginate–TiO_2 beads would be used in the near future for developing a new generation of multifunctional green catalysts.

4.1.3 Ammonium Nitrogen Removal

Ammonium nitrogen (NH_4^+–N) is an aquatic plant nutrient that when present at high concentrations yields an eutrophication evapotranspiration rate process. This represents a serious environmental problem, making necessary the removal of NH_4^+–N from water. Zeolites and molecular sieves have been traditionally used to remove NH_4^+–N, although their adsorption capacity remains too low to satisfy the effective demand. Zhen et al. showed that chitosan-*graft*-poly(acrylic acid) hydrogels reinforced with rectorite clay effectively remove NH_4^+–N within 3–5 min with a adsorption capacity as high as 123.8 mg/g [108]. Note that the maximum adsorption capacity is notably larger than those reported for common adsorbents for NH_4^+–N such as mesoporous zirconium dioxide (29.7 mg/g) or aluminum oxide (35 mg/g) [115, 116].

4.1.4 Adsorbent to Remove the Rare–Earth Elements (REEs)

Nowadays, rare-earth elements (REEs) are being currently used in many high-technology applications, and their separation and purification represent several

disadvantages such as high energy consumption, low selectivity, high cost, and generation of secondary metabolites [117].

In a recent work, Xu et al. [118] evaluated the selective adsorption capacity of 15 types of RREs (in single and mixed aqueous solutions) of a gel particle material fabricated through the immobilization of sodium alginate (SA) with poly-γ-glutamate (PGA). Results reveal a pivotal role of both the carboxyl groups (through a cation exchange between the –COOCa and R^{3+}) and porous structure of hydrogels on the adsorption capacity of the resulting materials, which showed a kinetics following a pseudo-second-order equation with a Langmuir adsorption isotherm model. Indeed, the adsorption was observed to occur as a spontaneous endothermic process. A beneficial role of poly-γ-glutamate toward the increase of the RRE adsorption efficiency in regard to neat sodium alginate was observed, which allows a superior mass transfer ability to reach a noteworthy value of 178.57 mg/g at 45 °C for La^{3+}. This adsorption capability was maintained after ten adsorption–desorption cycles, indicating the potential of these materials for water purification purposes. Another strategy to adsorb RREs and remove these polluting elements form the environment is to incorporate them into the hydrogel structure. In this context, Shunli et al. [119] used a rare-earth coordination bonding in order to crosslink *N*-succinyl chitosan and sodium alginate. More specifically, Gd^{3+} and Yb^{3+} lanthanide ions were used to develop nacre-like high-toughness and highly transparent hydrogels after the coordination of the carboxyl groups of *N*-succinyl chitosan and sodium alginate.

Zhu et al. [120] reported a simple approach to develop a hybrid granular hydrogel through a grafting reaction of acrylic acid onto hydroxypropyl cellulose backbone (HPC, an ether of cellulose), with attapulgite as the inorganic component. The role of attapulgite is to provide a large specific surface area and moderate cation exchange capacity of the whole structure. Results reveal fast absorption kinetics of La^{3+} and Ce^{3+}, where more than 90% of the adsorption capacity was achieved within initial 30 min (the adsorption rate was dependent on the rate at which the metal ions were transported from the bulk liquid phase to the actual adsorption sites). Being the carboxyl groups the main functional groups for the adsorption of REEs, by increasing the APT content, an appreciable decrease in the adsorption capacity was observed. This removal efficiency was pH-independent at pH $\geq$ 4.0, and it was correlated to the strong interaction between the La^{3+}/Ce^{3+} ions and the functional group hydrogel via coordination linkages, making it interesting to be used as a very effective adsorbent for the removal of La^{3+} and Ce^{3+} from aqueous solution.

Reusability studies were further carried out using HCl because the interaction between carboxylate and La^{3+} and Ce^{3+} could be weaken and, subsequently, La^{3+} and Ce^{3+} ions are released from the adsorbent into the desorbing medium. It is observed in Fig. 8 that the desorption ratio could be as high as 90% for La^{3+} and 85% for Ce^{3+} (in less than 1 h), being the adsorption capacity after five consecutive adsorption–desorption cycles slightly decreasing by 15%. These excellent reusability characteristics together with their absorption capacity suggest that these hybrid SAHs are very effective adsorbents for the effective removal of REEs.

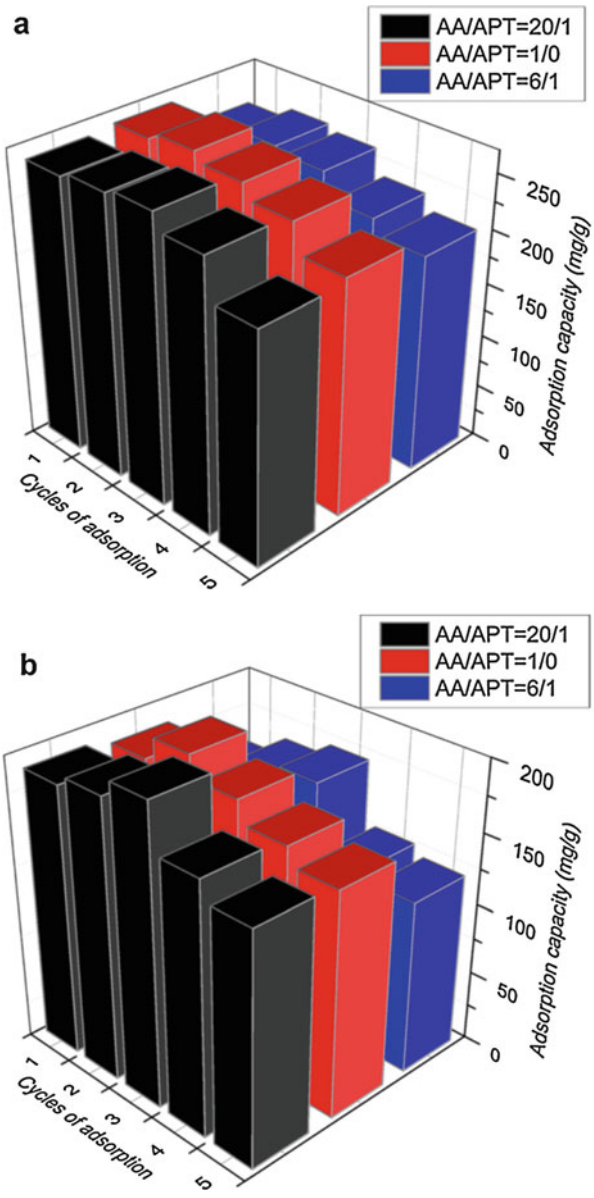

Fig. 8 The amount adsorbed for REEs as a function of adsorption–desorption cycle: La(III) **(a)** and Ce(III) (**b**). (Reproduced with permission from Ref. [120], Copyright (2015), Elsevier)

4.2 Biomedical Applications

Thanks to their high water content, porosity, soft consistency, biocompatibility, and biodegradability (if proper materials are selected), hydrogels simulate many features of living tissues, making them especially suitable for a wide range of biomedical applications.

4.2.1 Antibacterial Applications

Traditionally developed hydrogels are composed by materials such as acrylic acid and acrylamide which show poor antibacterial properties. It has been widely reported that the antibacterial activity of SAHs could be improved through the incorporation of silver nanoparticles [104], leading to non-desirable effects such as argyria (skin discoloration) [121]. In this framework, several authors have focused their efforts to the synthesis of biodegradable and biocompatible SAHs with antibacterial properties. To that end, quaternary ammonium chitosan-*graft*-poly (acrylic acid-*co*-acrylamide) SAHs were recently prepared by He et al. [4]. Quaternary ammonium chitosan hydrogels present good biocidal activity against *Escherichia coli (E.coli*) and *Staphylococcus aureus* (*S. aureus*) as a result of the mutual attraction between the positive charge of quaternized chitosan and the negative charge of microbial cell membrane surface, which damages the cell membrane [104].

4.2.2 Drug Delivery Systems (DDS)

The inherent porous structure of hydrogels allows the loading and posterior release of different drugs, allowing to obtain a sustained release over a long period of time [122]. Two different types of DDS could be prepared: diffusion-controlled release systems and swelling-controlled release systems. The topical applications of SAHs loaded with drugs have been proven to effectively alleviate the symptoms of several pathological conditions and are usually applied via the following routes: ocular, peroral, transdermal, vaginal, or rectal [123].

For example, superabsorbent hydrogel with excellent pH-sensitive behavior and On–Off switching swelling characteristics was developed by free-radical solution polymerization in the presence of initiator ammonium persulfate (APS) and crosslinker *N,N′*-methylene-bis-acrylamide [13]. Obtained semi-interpenetrating polymer networks of sodium alginate-*graft*-poly(sodium acrylate) (NaAlg-*graft*-PNaA) network and linear poly(vinyl pyrrolidone) display a large swelling capacity at pH 7.2 that could be rapidly shrunken at pH 2 (in about 1 min). These characteristics were maintained barely unchanged after five On–Off cycles, which could be potentially used for DDS. Composite SAHs with excellent responsive physicochemical properties and reversible On–Off switching characteristics depending on the surrounding pH have been as well obtained by the grafting copolymerization of natural guar gum (GG) and partially neutralized acrylic acid (NaA) in the presence of medicinal stone (MS) micro powder using ammonium persulfate as the initiator and *N,N′*-methylene-bis-acrylamide (MBA) as the crosslinker [71]. MS is a class of igneous rock composed of more than 50 types of trace elements ($KAlSi_3O_8$, $FeAl_2Si_2O_8$, $CaAl_2Si_2O_8$, etc.) which presents a unique porosity and biological activity. Environmentally friendly inorganic MS participates during the polymerization through its active silanol groups, yielding improved stability to the GG-*graft*-PNaA/MS superabsorbent composite. For instance, water absorption is enhanced by 96% after the addition of 10 wt.% of MS.

4.2.3 Wound Dressings

An ideal wound management product must be able to keep a proper moisture, protect the wound from infection, absorb toxin excess, have good permeability to gases, and be easy to remove [124]. Plain gauze is one of the most commonly employed wound dressings in hospitals, which is often impregnated with zinc oxide, iodine, or petrolatum. To avoid the problems associated with dressing removal and to ensure a better moisture capture, hydrocolloid dressings based on pectin, carboxymethylcellulose, or gelatin have been developed. Some examples of commercially available products are Intrasite Gel® (Smith & Nephew), Purilon Gel® (Coloplast), Hydrofiber® (ConvaTec), Granugel® (ConvaTec), or Woundtab® (First Water) [123].

4.2.4 Tissue Engineering

Tissue engineering (TE) is aimed to improve or replace specific tissues and organs using engineered materials [125]. Both synthetic and naturally occurring materials could be used for developing hydrogels for TE applications. Hyaluronic acid, agarose, chitosan, gelatin, and alginate are some of the most commonly employed polysaccharides [126]. Polysaccharide-based injectable scaffolds were combined with biological molecules for the fabrication of components that repair/regenerate the hyaline cartilage. As depicted in Fig. 9, this has been attempted by using hydrogels as in situ forming scaffolds and bioprinting techniques [127]. Some examples include the synthesis of keratin-based hydrogels for the development of three-dimensional porous structures or scaffolds using a UV crosslinking in a lithography-based 3D printer [128], photoresponsive hydrogels obtained by coordination of alginate−acrylamide gels with ferric ions (where the photochemical treatment is able to modify extracellular matrix growth and chondrogenic cell production) [129], semi-interpenetrating networks composed of hyaluronic acid and (poly(2-hydroxyethylmethacrylate-*co*-2-methacryloxyethyltrimethylammonium)) (p(HEMA-*co*-METAC)) with good cytocompatibility with mouse fibroblast and improved cell adhesion [130], collagen-based hydrogels for cartilage and skin repair [131, 132], and so on.

4.2.5 Hygiene Products

Because of their water retention ability, hydrogels were introduced into the diaper industry more than 30 years ago. The first feminine napkin composed by crosslinked starch-*graft*-polyacrylate was commercialized in Japan in 1978 [16]. Since then, a plethora of systems based on both synthetic and natural materials have been developed for hygienic applications. One of the main concerns in this industry is the large volume of disposed hygiene products (an average child produces 1092 m^3 of waste in the form of disposable diapers) [133]. Therefore, obtaining SAHs that undergo biodegradation becomes essential for the modern industry. Environmental friendly products based on cellulose emerge as a plausible alternative to obtain totally biodegradable goods. These hydrogels consist of materials such as hydroxyethyl cellulose (HEC), crosslinked with divinyl sulfone (DVS), and sodium carboxymethylcellulose (NaCMC) and have been proven to possess a higher water retention capacity as a result of the capillary effects [133]. Due to their high swelling capacity,

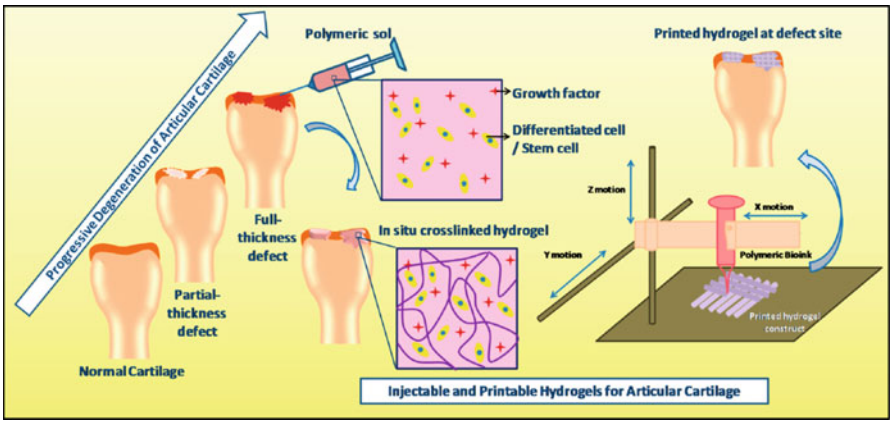

Fig. 9 Schematic representation of progressive degeneration of articular cartilage, where white patches in superficial cartilage tissue represent partial-thickness defects and red patches denote the full-thickness defect. In situ forming hydrogel that fills the irregular osteochondral defect serves as depot for cells and encapsulated growth factors. (Reproduced with permission from Ref. [127], Copyright (2017), American Chemical Society)

many of the polysaccharide-based SAHs shown through this chapter could also potentially be used for the development of disposable absorbent articles such as diapers and sanitary napkins.

4.3 Agricultural Applications

Over the last years, SAHs have also been investigated for agricultural applications as soil conditioners and as carriers for controlled nutrient release such as fertilizers. Owing to their excellent biocompatibility and biodegradability, low-cost, eco-friendly nature and abundance, polysaccharide-based SAHs are especially interesting for these applications. The high water absorption capacity of these structures enables the reduction of irrigation water consumption and improves the physical properties of the soils (SAHs act as water reservoir which releases water in a controlled fashion) [6].

The loading (into SAHs) and subsequent controlled release of fertilizers (from the SAHs) to the soil may prevent the usual loss of fertilizers by leaching. Although the hydrogels could be loaded with nutrients by two different approaches, in situ loading (during processing) and *post*-loading (after hydrogel processing), the first one is preferred because it allows higher loading efficiencies [134]. Nutrient release is activated by the swelling of the SAH during irrigation or raining, where the permeant water dissolves the nutrient to diffuse to the outside medium [135, 136]. The release is stopped when the hydrogel dries and is further activated upon watering process, providing sustained release of nutrients, which is especially interesting for deserted areas. Different systems have been used to that end, such

as carbodiimide-crosslinked cellulose SAHs [137], saponified cassava starch-*graft*-poly(acrylamide) [138], or pectin-modified SAHs for the release of phosphate, potassium, and urea [69]. More examples include alginate-based SAH for neem seed oil release [139], ionically crosslinked carboxymethyl-cellulose SAH for root-directed release [140], and sodium carboxymethylcellulose/hydroxyethylcellulose SAH for nitrogen-containing fertilizer release [141].

Salt could as well be introduced into SAHs for their controlled release. For instance, Hua et al. [7] synthesized sodium alginate-*graft*-poly(acrylic acid)/sodium humate (NaAlg-*graft*-PAA/SH) superabsorbent hydrogels by graft copolymerization reaction in aqueous solution, using *N,N′*-methylenebisacrylamide as a crosslinker and ammonium persulfate as an initiator. Results showed that these SAHs present an absorption capacity up to 1380 g/g in distilled water and 83 g/g in 0.9 wt.% NaCl solution and at the same time that they could selectively release sodium humate (SH). SH contains carboxylates and phenolic hydroxyls in its structure and can regulate plant growth, accelerate root development, enhance photosynthesis, improve soil cluster structures, and benefit the absorption of nutrient elements. Therefore, these SAHs could be used as water-holding elements for the soil (especially interesting in arid environments) and at the same time that released SH serves as a nutrient for plant growth.

Nanocomposite SAHs have also been developed for agricultural applications. For example, sodium alginate-*graft*-poly(acrylic acid-*co*-acrylamide)/rice husk ash superabsorbent nanocomposite hydrogels were synthesized by the free-radical graft copolymerization of NaAlg, AA, AAm, and RHA in aqueous solution for water management (and plant feeding) in agricultural and horticultural applications [76]. These SAHs present an equilibrium swelling capacity of 1070 g/g when compared to the 830 g/g of neat hydrogel as a result of the higher porosity and the stronger electrostatic repulsive forces of RHA with the carboxylate groups of hydrogel, which enhances the swelling capacity. Moreover, SH/RHA showed excellent pH-dependent swelling reversibility behavior over a wide pH range, good salt resistance, and good reswelling. Overall, experimental findings reveal that the release profile could be tuned after the introduction of particles into hydrogels, which disturbs the solute release via tortuosity enhancement, retarding fertilized release [142, 143].

4.4 Building Applications

Automatic self-healing of concrete is a promising approach to reduce the cost of building maintenance and repair cracks with no human intervention. In this sense and taking advantage of the swelling capacity of hydrogels, Mignon et al. prepared SAHs with pH-sensitive self-healing properties that could be used for the self-sealing of cracks in buildings using three different polysaccharides as starting materials [35]. Alginate, agarose, and chitosan were successfully methacrylated to obtain a DS of 37.8%, 14.19%, and 6.59%, respectively, and were subsequently crosslinked with two amine-based monomers, dimethylaminoethyl methacrylate (DMAEMA) and dimethylaminopropyl methacrylamide (DMAPMA). Alginate and chitosan were

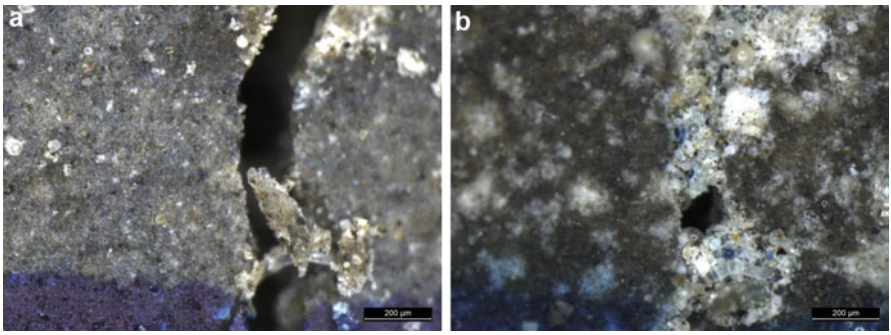

Fig. 10 Microscopy images showing a partial self-sealing of cracks up to 200 µm. (a) Before water infiltration and (b) once water has been infiltrated and the SAH is swollen. (Reproduced with permission from Ref. [35], Copyright (2017), Elsevier)

used because they show an opposite pH sensitivity in alkali conditions, while DMAEMA and DMAPMA present a different pKa value. This allows the tailoring of swelling properties of developed materials. As a result of the introduction of DMAEMA and DMAPMA monomers, synthesized SAHs display a pH-responsive behavior. This pH sensitivity has been used to develop smart materials that after being incorporated into a fresh mortar (which has a pH of about 12.5–13) could seal cracks. At such a high pH value, the hydrogel presents a very low swelling capacity, creating small macropores across the hardened concrete. Once the concrete is settled and after crack formation, the water (having a pH closer to neutral value) enters the newly formed crevice, and it is absorbed by the SAHs, which would eventually swell to seal the crack, thereby improving the durability of the structure. More precisely, authors have shown that cracks up to 200 µm could be partially sealed when methacrylated agarose and chitosan combined with DMAPMA are introduced in the concrete structure (Fig. 10). Similarly, microcapsules with high swelling capacity based on gelatin–acacia gum and sodium silicate [144] and modified alginate-based hydrogel with incorporated *Bacillus sphaericus* bacterium have also been prepared for achieving concrete with automatic self-healing properties [145].

5 Conclusions

Polysaccharides have been successfully employed in the development of superabsorbent hydrogels. This chapter reviews the main synthetic methods used in this field to obtain the different types of polysaccharide-based SAHs. Also, the properties of these materials have been summarized, describing the variation on the swelling capability with the change of the media, their thermal and mechanical properties, and their biodegradation. In addition, their properties make them suitable for a wide variety of applications such as water treatment, biomedicine, agriculture, and building applications.

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Biodegradable Hydrogels for Controlled Drug Delivery

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Contents

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Abstract

Hydrogels are three-dimensional cross-linked polymeric networks that can imbibe large amount of water or biological fluids. The ability of hydrogel to absorb water appears due to the presence of hydrophilic groups such as –OH, –CONH, $–CONH_2$, –COOH, and $–SO_3H$, along the polymer chain. Depending on the pendant functional groups, hydrogels have the ability to respond to their environmental changes such as pH, ionic strength, or temperature. The high water content and soft texture of these hydrogels translate them into a biocompatible material. This property renders the hydrogel similar to biological tissues and consequently minimizes inflammation once implanted or injected in the body. Biodegradable hydrogels are further adding advantages of degradation of the matrix into innocuous biocompatible products that can be eliminated after serving, thus eliminating the necessity of their removal. The degree of biodegradation can be controlled by manipulating the cross-linking with suitable precursors. Their mechanical property can also be tailored to have structural stability followed by extended release of cargo molecules. Their flexibility and minimally invasive administration are useful characteristics for their increased application in biomedical fields. Biodegradable hydrogels as controlled release systems are investigated to improve the temporal and spatial presentation of drug in the body, to protect drug from physiological degradation or elimination and to improve patient compliance. Hence the author has made an attempt to discuss biodegradable polymers of natural and synthetic origin, the biodegradation mechanisms, hydrogel engineering strategies, drug-hydrogel interactions, and release kinetics and mechanisms of such hydrogels to attain controlled delivery of drugs to different site of action in this chapter.

Keywords

Biodegradable polymers · Biodegradation mechanism · Hydrogel preparation methods · Drug-hydrogel interactions · Release kinetics and mechanisms

1 Introduction

Biodegradable hydrogels are cross-linked three-dimensional structures that are capable of being broken down into less complex innocuous products which are eliminated from the body. These hydrogels are engineered with materials that are susceptible to cleavage either by hydrolytic or enzymatic means. A large number of polymers from natural and synthetic origin have been employed to design such structures. Polymer chains with optimized hydrophilic and hydrophobic domains can result into a hydrogel of suitable mechanical strength. Polymer chemistry largely influences the hydrogels biodegradation rate. Biodegradation process deteriorates the structural integrity of the matrix allowing the release of immobilized cargo molecules. Diverse methodologies are available to design such hydrogels to serve the purpose of controlled drug delivery. The unique features like swelling, biocompatibility, and

most importantly biodegradability of hydrogels not only control the drug release but also able to bypass their surgical removal after serving. Hence, the author has made an attempt to discuss such a vital delivery device which could be used successfully to attain temporal and spatial release of drugs and other bioactive molecules.

2 Properties of Hydrogel

Hydrogels are the classic biomaterials endowed with very exciting properties. Their in-vivo swelling property, mechanical strength, and the compatibility with the biological tissues have attracted considerable attention of the scientific fraternity, for their application in the field of pharmaceutical and biomedical engineering [1, 2]. These biomaterials are explored as a courier to deliver drugs and other therapeutic biomolecules of interest in a controlled mode. To meet contemporary challenges, investigations are focused to fabricate hydrogels with tailorable properties so that the temporal and spatial presentation of drug in the body improves as well as the bioactive therapeutic molecules could be protected from physiological harsh conditions and/or degradation and improves patient compliance. This section deals with three such important properties of hydrogel.

2.1 Swelling Property

Hydrogels are engineered biomaterials developed by physical or chemical cross linking of polymer moieties. For this reason, there is no concept of molecular weight of hydrogels and therefore, sometimes called infinitely large molecule or super macromolecule. When these hydrogels comes in contact with aqueous environment, they start to imbibe water or aqueous fluids without dissolving in it. The swelling continues till the polymer-water interactions are opposed by polymer-polymer interactions. In other words, the elastic activity resulting from polymer-polymer interactions prevents the water flux inside the hydrogel resulting in a state of affair called equilibrium swelling. The degree of equilibrium swelling and the elastic modulus of hydrogel could be tuned depending on the cross-linking and charge densities of the polymer network, and the concentration of the polymer involved in such formation. In case of hydrophilic polymer network, water acts as a plasticizer and the swelling of the hydrogel can be explained under the rubbery elastic state. The swelling of the hydrogel system, ΔG_{System} can be explained by the free energy of mixing, ΔG_{mix} resulting from the polymer-solvent interaction; and the elastic free energy, $\Delta G_{elastic}$ resulting from the cross-linked polymers interaction [3].

$$\Delta G_{System} = \Delta G_{mix} + \Delta G_{elastic}$$

At the time of swelling inception, the $\Delta G_{mix} \ll 0$ and $\Delta G_{elastic} > 0$. So, $\Delta G_{mix} + \Delta G_{elastic} < 0$ and the swelling is favored and the solvent diffuses inside the network. During the swelling process, both the ΔG_{mix} and $\Delta G_{elastic}$ increases

until $\Delta G_{mix} = \Delta G_{elastic}$ and the $\Delta G_{System} = \Delta G_{mix} + \Delta G_{elastic} = 0$. As the driving force for swelling declines, the equilibrium swelling of the hydrogel is established.

Instrumental parameters like pH, temperature, electrical signal, or increasing number of ionic groups may lead to a swelled physical texture of hydrogel. These changes may be observed at macroscopic level. The concentration gradient of mobile ions in the interior and exterior hydrogel environment, call for osmotic pressure change resulting in a swelled hydrogel. Hydrogels with acidic or basic pendant functional groups also respond to the surrounding pH fluctuations. The degree of ionization of such groups dictates the swelling profile and volume transformation. Similar volume transformation behavior can be observed when the carboxyl groups of polyacrylic acid (PAA) hydrogel ionized in response to the surrounding pH. Hydrogels modified with hydrophobic moieties exhibit thermo-sensitive swelling behavior. Above the lower critical solution temperature (LCST), certain hydrophobic moieties respond and separate them from the solution to take a de-swelled or collapsed form. That means above this threshold temperature, i.e., LCST, hydrogels become increasingly hydrophobic and starts to collapse. That means above LCST, certain polymers undergo phase transition from a soluble to an insoluble state. Below the LCST, the polymers remain soluble and exhibit an expanded/swelled hydrogel [4]. LCST-based volume-phase transitions are most common in co-polymer hydrogels. Such transition is primarily attributed to the type and amount of monomer incorporated in the hydrogel formation. The presence of increasing amount of hydrophilic monomers raises the LCST, in contrary to the hydrophobic monomers which in practice lowers the LCST. That means the hydrogels rich in hydrophilic monomers will de-swell at higher temperature and the hydrogels rich in hydrophobic monomers will de-swelled at relatively lower LCST. By optimizing the hydrophilic and hydrophobic monomers ratio, swelling "on-off" behavior can be controlled.

2.2 Mechanical Property

Mechanical properties of hydrogels are very vital and critical from pharmaceutical and biomedical point of view. Optimum mechanical strength of a hydrogel is a prerequisite for their successful implementation as a drug delivery device. The optimal mechanical property of hydrogels would be such that its physical texture is maintained till the cargo molecules are released at a predetermined rate for a predetermined time. Optimal degree of cross-linking may lead to a hydrogel with suitable mechanical strength. However, by increasing the degree of cross-linking, a stronger hydrogel may be developed with brittle-featured hydrogel exhibiting decreased % elongation. Hence, it is desirable to optimize the degree of cross-linking to achieve relatively stronger and yet elastic hydrogel. On the basis of young's modulus and Flory's theory, it is possible to determine the cross-linking density of hydrogels [5]. For the evaluation of hydrogels mechanical property, the young's modulus, tensile and compression strength, and the swelling ratios remain the gold standards. Hydrogels produced with synthetic polymers typically exhibit low young's

modulus (1–100 kPa), low tensile and compression strength (1–100 kPa), low fracture energy (<10 J/m^2) but still retains high swelling ratio (10–100). Normal stress-relaxation experiments are generally adopted to determine the viscoelastic behavior of hydrogel.

2.3 Biocompatible Property

For the successful application of hydrogels in the biomedical field, it must be compatible and nontoxic to the biological cells and tissues. Most polymers used for this purpose must pass cytotoxicity and in-vivo toxicity tests. Biocompatibility is the ability of the hydrogel to perform an appropriate host response in a specific application. Biocompatibility basically consists of two elements: (a) biosafety, i.e., appropriate host response from both systemically and locally in the surrounding tissue; absence of cytotoxicity, mutagenesis, and/or carcinogenesis and (b) bio-functionality, i.e., the ability of hydrogel to perform the specific task for which it is intended. This definition is particularly relevant in tissue engineering since the nature of tissue construct is to continuously interact with the body through the healing and cellular regeneration process as well as during scaffold degradation. If this requirement is not met, the hydrogel can be fouled or there may be damage and scarring to connected tissues, whether those tissues are immediately adjacent or linked by vasculature. Toxic chemicals that are sometime used in the polymerization of synthetic hydrogels present a challenge for in-vivo biocompatibility, if they are not converted 100%. Furthermore, initiators, organic solvents, stabilizers, emulsifiers, unreacted monomers, and cross-linkers used in polymerization and hydrogel synthesis may be toxic to host cells if they seep out to tissues or encapsulated cells [6]. Though natural polymers extends superior biocompatibility over the synthetic counterparts, the utilization of synthetic cross-linkers and initiators in the polymerizations of naturally derived monomers and pre-polymers are again subject to the same toxicity concerns as applicable for purely synthetic hydrogels. However, there are certain methods available like solvent washing or dialysis to purify the preformed gels.

3 Biodegradable Hydrogels

Biodegradable hydrogels are cross-linked three-dimensional structures that are capable of being broken down into less complex innocuous products by the action of solubilization, chemical hydrolysis, enzymatic hydrolysis, or other biologically formed entities. The engineering of such hydrogels make them susceptible to cleavage either by hydrolytic or enzymatic means. The labile materials like cross-linkers and pendant functional groups are the building blocks of hydrogel architecture. Biodegradable hydrogels possess huge potential for biomedical application like controlled drug delivery. They are advantageous because they degrade in-vivo and there is no need for their removal after the useful life span.

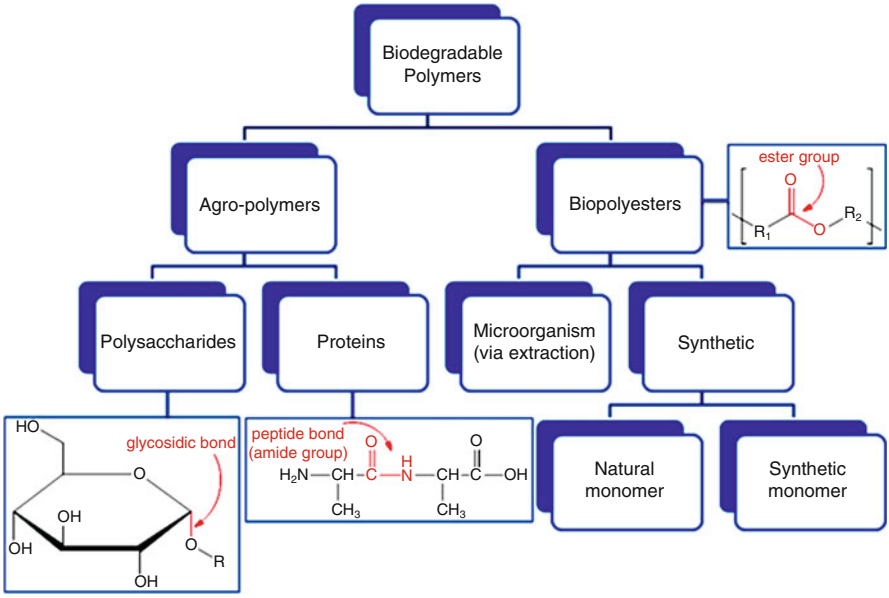


Fig. 1 Biodegradable polysaccharide, protein, and bioester polymers indicating cleavable bonds

3.1 Biodegradable Polymers

Biodegradable polymers are the materials that functions temporarily and subsequently degrade in a controlled fashion into a less complex material that are eliminated by the body's metabolic pathway. This kind of polymers eliminates the risk associated with long-term presence of foreign material that may call for its surgical removal. Biodegradable polymers degrade in-vivo, either by enzymatic or non-enzymatic means and transform into a biocompatible, innocuous, or nontoxic by-products. Hence, the biodegradable polymers should be capable of controlled degradation rate while maintaining mechanical integrity to satisfy the purpose of controlled drug delivery. The factors that contribute to the biodegradation are molecular weight, percentage of crystallinity, and hydrophobicity of the polymer. The rate of biodegradation also depends on the pH, enzyme concentration and the quantity of water in place. Broadly the biodegradable polymers are of two types; natural and synthetic. So, apparently the formation and functioning of biodegradable hydrogels would depend on the type and composition of the polymer. In Fig. 1, an illustration is presented which indicate the cleavable bonds of biodegradable polysaccharide, protein, and bioester type polymers.

3.1.1 Natural Biodegradable Polymers

Natural polymers, such as fibrin, collagen, gelatin, albumin, alginate, dextran, glycosaminoglycan, chitosan, starch, hyaluronic acid, and cyclodextrins are

comparatively hydrophilic and malleable materials that offer flexibility to adapt a particular shape [7].

3.1.2 Synthetic Biodegradable Polymers

Synthetic polymers represent the largest biodegradable group and are produced under controlled provisions. For example, poly(orthoesters) are synthetic plant polysaccharide produced by polycondensation of a diol (i.e., either 1,6 hexanediol/cis/trans 1-4-cyclohexane dimethanol) with an orthoester (i.e., diethoxy tetrahydrofuran). Polyanhydries are another class of synthetic polysaccharide produced from dicarboxylic acids such as adipic acid, sebacic acid, etc. Such type polymers exhibit predictable and reproducible mechanical and physical properties like tensile strength, elastic modulus, and degradation rate. These polymers are classified and represented below [8]:

(i) **Aliphatic Polyesters**: Poly(lactic acid) (PLA), Poly(glycolic acid) (PGA), Poly(lactide-co-glycolide) (PLGA), Poly(ε-caprolactone) (PCL), Poly (p-dioxanone), Poly(hydroxyl butyrate) (PHB), Biopol (polyhydroxybutarate-hydroxyvalerate), Poly(β-malic acid)
(ii) **Poly(phospho-esters)**: Poly(phosphates), poly(phosphonates), poly (phosphazenes)
(iii) **Poly(anhydrides)**: Poly(sebacic acid), poly(adipic acid), poly(fumaric acid), poly(terephthalic acid), poly(erucic acid)
(iv) **Poly (amides)**: Poly(imino carbonates), e.g., [(Phenyl)azo]phenyl]*imino*]bis-ethyl-methyl-*carbonate* and Poly(aminoacids), e.g., poly(L-glutamine)
(v) **Poly (ortho esters)**: Poly(orthoesters)-I with cis/trans-cyclohexyldimethanol, Poly(orthoester)-II with 1,6-hexanediol

The molecular structure of few important synthetic monomers and polymers are presented in the Table 1:

3.2 Preparation of Biodegradable Hydrogels

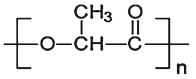
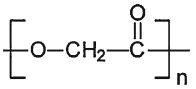
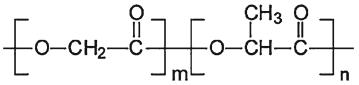
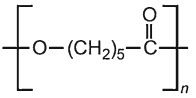
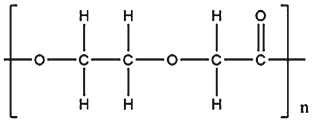
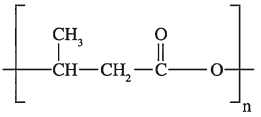
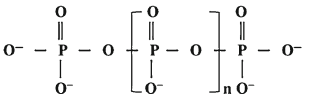
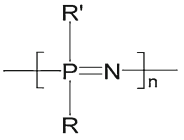
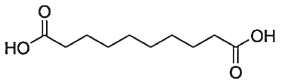
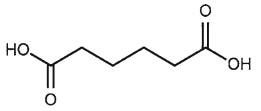
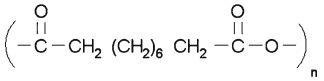
3.2.1 Physically Cross-Linked Hydrogels

Physically cross-linked hydrogels can be achieved by variety of physicochemical interactions like hydrophobic interactions, charge interactions, hydrogen bonding, stereo-complexation, and supramolecular chemistry.

Hydrophobic Interactions

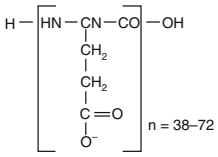
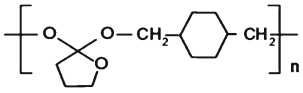
Hydrophobic segments of a polymer are capable of transforming from a sol state to a cross-linked gel state in aqueous environment via reverse thermal gelation process. The polymers with such gelation properties are referred to as gelators. A gelator can be fixed with a polymer containing hydrophilic segment by post-polymerization grafting or by synthesizing block copolymer to create polymer amphiphiles. Such amphiphiles show significant water solubility at low temperature. However, as the

Table 1 Molecular structures of few synthetic biodegradable monomers and polymers

Type of polymer	Name of the polymer	Molecular structure
Aliphatic polyesters	Poly(lactic acid)	
	Poly(glycolic acid)	
	Poly (lactide-co-glycolide)	
	Poly(ε-caprolactone)	
	Poly(p-dioxanone)	
	Poly(hydroxyl butyrate)	
Poly(phospho-esters)	Poly(phosphates)	
	Poly(phosphazenes)	
Poly (anhydrides)	Sebacic acid	
	Adipic acid	
	Poly (sebacic anhydride)	

(*continued*)

Table 1 (continued)

Type of polymer	Name of the polymer	Molecular structure
Poly (amides)	Poly (L-glutamic acid)	
Poly (orthoesters)	Poly(Orthoester)	

temperature rises, the hydrophobic domains starts to aggregate with the aim to minimize the contact between hydrophobic surface and water. This reduces the amount of structured water surrounding the hydrophobic domain. The appearance of gel state at a particular temperature also depends on the concentration, length of hydrophobic segment, and the chemical structure of the polymer. If the polymer contains more hydrophobic segment, the driving force for hydrophobic aggregation will be more resulting the gel formation at lower temperature.

Poloxamers popularly known as pluronics are the triblock copolymers of poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) (PEO-PPO-PEO). They are mostly used polymers that display reversible thermo-gelation behavior. An aqueous solution of poloxamer-407 (25% w/v), containing ~101 repeating units in each PEO block and ~56 repeating units in each PPO block, is viscous at room temperature but forms a hydrogel at body temperature of 37 °C [9]. Poloxamer-407 has been investigated to extend the lidocaine release. The polymer solution containing the drug was developed at lower temperature and then injected where the body temperature transformed it into a gelled structure, resulting in prolonged drug release [10]. However, there are few reports which reveal the rapid dissolution of poloxamers in-vivo due to the water influx resulting in polymer dilution. This impediment can be overcome by the incorporation of ethoxysilane groups in the PEO-PPO-PEO triblock. In course of time, this ethoxysilane hydrolyzed to form silanol which covalently cross-link the network thus preventing its rapid dissolution [11]. In another study, poloxamer equipped with amine functional group can be grafted on hyaluronic acid to form self-assembled carbohydrate-rich network which slows down the release of ciprofloxacin and human growth hormone [12, 13]. This type of graft network exhibit reduced dissolution rate primarily attributed to the high viscosity of hyaluronic acid graft. Penta-block PDMAEMA-PEO-PPO-PEO-PDMAEMA is a modified version of poloxamer. It forms free flowing liquids at room temperature, but when heated, they behave as elastic hydrogels at concentrations above 12%. This facilitates the release of sparingly soluble drugs at the rate nearly zero order [14]. Amphiphile polymers can be used

successfully as an alternative to poloxamers. Biodegradable tri-block co-polymers of polylactic acid, polyglycolic acid are mostly used as an alternative to poloxamers. These PLGA-based gelators are more biodegradable; easy to handle before injection, i.e., high gelation temperature; and support prolonged drug release. This PLGA hydrophobic domain may be inserted in the center of the block (e.g., PEG-PLGA-PEG) or in the terminal of the block (e.g., PLGA-PEG-PLGA). The release of hydrophilic drugs from such matrix was found to follow diffusion controlled mechanism [15, 16]. However, the release of hydrophobic drugs initially followed diffusion controlled mechanism and later on by polymer degradation controlled mechanism [17].

Poly-*N*-isopropylacrylamide (PNIPAM) is a synthetic thermo-responsive polymer widely investigated for prolonging the drug release. The gelation of this polymer occurs at lower concentration. PNIPAM-poly(phosphorylcholine)-PNIPAM tri-block co-polymers have been reported to form gels at 6–7 wt% when the temperature exceeds 32 °C [18]. Physically cross-linked PNIPAM hydrogel can also be prepared by grafting them on natural polymers like hyaluronic acid. Such matrix found to display burst release of riboflavin for first 12 h and thereafter sustained release profile [19]. Polycaprolactone (PCL) or PCL-glycolic acid co-polymers are combined with polyethylene glycol (PEG) to form tri-block network to facilitate prolonged release. PEG-PCL co-polymer network released the FITC-labeled bovine serum albumin over the period of 30 days owing to the lower water content and longer network stability [20]. Synthetic thermoresponsive polymers like polyorganophosphazene are reported to produce mechanically stronger gels at lower concentration. A suitable modification of polyorganophosphazenes with hydrophobic, hydrophilic, and biodegradable moieties can extend the release of Doxorubicin for a period of 1 month [21]. Polyurethanes are also known to form gel by hydrophobic interactions. Natural polymer like chitosan conjugated with glycerol-2-phosphate undergoes reversible thermo-gelation at nearly 37 °C [22]. Chitosan grafted with PEG gelled at 37 °C and released bovine serum albumin for 70 h followed by initial burst release [23]. Hydroxypropylcellulose and methylcellulose are reported to demonstrate thermally induced gelation.

Charge Interactions

Charge/ionic interactions are also used to develop physically cross-linked hydrogel in-situ. Such hydrogels degrade in-vivo by the replacement of its structural components by ionic species of extracellular fluid. Alteration of environmental pH influences the ionization or protonation of the ionic functional groups, which may favor cross-linking and gelation. Charge interactions may exist between polymer and "elastin" like small molecule or in between two oppositely charged polymers translating into a hydrogel. Peptides equipped with alternating positive and negative charge, self-assemble to form hydrogels in-situ. Charge interactions are made to fabricate micro or nanoparticle embedded 3D matrix [24]. Similar type interaction can also be seen in case of dextran microspheres coated with oppositely charged polymers. When the microspheres coated with anionic polymer mixed with cationic polymer, gelation occurs spontaneously and the microspheres get embedded.

Hydrogen Bonding Interactions

Hydrogen bonding interactions are widely used to produce polyvinyl alcohol-based physical hydrogels. These hydrogels are formed by the active participation of hydrogen bonding in freeze-thaw process in-vitro [25]. Hydrogels for the purpose of injection can also be formulated by this interaction. Hydrogen bond imparts a different degree of visco-elasticity to a blend of natural polymers and translates them to behave more like a gel than those of the individual counterparts. When the shear stress is applied, i.e., the blend is forced to pass through the needle, relatively weak hydrogen bonds disrupt and facilitate the injection. Blends of natural polymers like gelatin-agar, starch-carboxymethyl cellulose, and hyaluronic acid-methylcellulose form physically cross-linked hydrogel involving hydrogen bonds. These hydrogels can be introduced into the body by injection. Such blends exhibit excellent biocompatibility due to the absence of chemical cross-linkers and because these natural polymers can imbibe huge amount of body fluid resembling extracellular matrix. However, the tendency of body water influx into these structures may be a reason for their rapid dilution in-vivo.

Stereo-Complexation

Stereo-complexation is a kind of physical force that occurs between polymer chains or small molecules of same chemical composition but different stereochemistry. This interaction results in an interlocking structure. A classic example of this type is enantiomeric lactic acids. This in-situ forming hydrogels are prepared by the strong interaction between poly-L-lactide and poly-D-lactide enantiomers. Multi-arm polyethylene glycol-polylactic acid (PEG-PLA) dendrimers are reported to produce cross-linked hydrogel using this stereo-specific interaction [26]. They exhibit transition temperatures ranging from 10 °C to 70 °C depending on polymer concentration and PLA block length. Natural polymers can also be cross-linked via stereo-complexing grafts. Grafting L-lactide and D-lactide oligomers to dextran precursor induces spontaneous gelation in water, resulting in excellent biocompatibility and biodegradability [27]. The application of stereo-complexation is restricted due to the limited availability of enantiomeric polymers. Moreover, very little change in polymer stereochemistry will significantly weak their interlocked structure or may even eliminate the stereo-chemical interaction.

Supramolecular Chemistry

Supramolecular chemistry is another approach to form hydrogel in situ. It is an orderly arrangement of molecules into a defined structure. The most common cross-linked structure in this category is the formation of inclusion complex. It can be observed between polyalkylene oxide polymers like polyethylene oxide (PEO) or polypropylene oxide (PPO) and cyclodextrins. Cyclodextrins are unique molecules equipped with hydrophilic surfaces and hydrophobic cavities which are geometrically compatible with PEO or PPO. A study reported the formation of supramolecular reversible injectable hydrogel from the interaction of PEO and α-cyclodextrin [28]. Similarly, β-cyclodextrin was also found to form hydrogel interacting with PPO grafted dextran [29]. Sometime, supramolecular chemistry along with hydrophobic

interaction is used to develop stable hydrogels. Self-assembled matrix formation from the interaction of PEO-poly-R-3-hydroxybutyrate (PHB)-PEO triblock copolymer with α-cyclodextrin is an example of this type. The cross-linking was materialized both by the thermal gelation of PHB hydrophobic segment and inclusion complex formation between PEO segment and cyclodextrin. This matrix was reported to release FITC-dextran for 1 month [30]. Recognition between naturally occurring macromolecules can lead to hydrogel formation in-situ. Interactions between heparin and polymer-grafted peptide which is extracted from heparin-binding proteins can rapidly form hydrogels. Such system display drug release kinetics and degradation profile depending on the affinity of heparin for heparin-binding peptide [31].

3.2.2 Chemically Cross-Linked Hydrogels

Physically cross-linked hydrogels have the advantage of forming hydrogels in-vivo without involving any chemical modification or addition of cross-linking agents. But these networks suffer from certain drawbacks. The most important of these are mechanical strength, gelation time, network porosity, degradation rate, etc., and all these depends on the chemistry of gelators. Thus to have superior control on these parameters, chemical cross-linking would be suitable answer. The most common type of chemical cross-linking encountered is discussed in this section.

Small Molecule Cross-Linking

Small molecule cross-linkers can be used to produce in-situ cross-linked hydrogels. Dextran-tyramine and hyaluronic acid-tyramine hydrogels are reported to use horse radish peroxidase and hydrogen peroxide as cross-linkers with very short gelation time [32, 33]. Human serum albumin was cross-linked with ester form of tartaric acid to develop a hydrogel to control the release of doxorubicin. Genipin has been used to cross-link amino functionalized polymers like polyethylene glycol (PEG), carboxymethyl chitosan, gelatin, and bovine serum albumin that exhibit minimal toxicity with tailorable dissolution rate upto 100 days. Certain cases have been observed where the drug molecule themselves took part into the cross-linking reaction. Primaquine is such an example of amine functional drug that cross-linked periodate-oxidized gum arabic via Schiff base formation, resulting from the reaction of drugs amine group and polymers aldehyde group [34]. The small molecule cross-linking in many cases associated with toxic manifestations due to the residual unreacted small molecule species. The example of glutaraldehyde can be enumerated here which is mostly used to form carbohydrate-based hydrogels.

Polymer-Polymer Cross-Linking

Suitably functionalized polymers have been used to develop polymer-polymer cross-linked hydrogels. Such networks avoid the use of potentially toxic small molecule cross-linkers. But this approach warrants significant modification of polymer chemistry. What type of linkage will be involved in polymer-polymer cross-linking depends on two factors (i) rapidity of linkage/bond formation and (ii) its biodegradability. The formation of hydrazone bond (asymmetric Schiff base) via the reaction

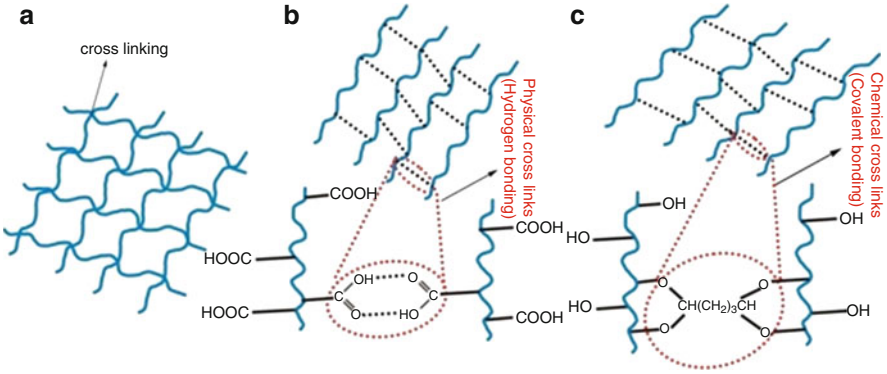


Fig. 2 (**a**) Hydrogel matrix; (**b**) physically cross-linked hydrogel matrix; (**c**) chemically cross-linked hydrogel matrix. (Adopted from Ref. [38])

between aldehyde and hydrazide facilitates the rapid cross-linking of hydrogel precursors. In a study, a cross-linked structure of hyaluronic acid was developed based on hydrazone bond. This network displayed prolonged effect of local anesthesia and controlled the release of tissue plasminogen activator and budesonide [35]. Dextran, polyvinyl alcohol and polyaldehyde guluronate precursor engineered hydrogels involve similar principle.

Michael addition between a nucleophile (i.e., an amine or a thiol) and a vinyl group is another widely investigated in-situ cross-linking chemistry. This type of reaction can produce rapidly cross-linked hydrogels that are flexible in forming different type of bonds. Michael addition reaction has been used to cross-link vinyl sulfone functionalized dextran with thiolated-PEG. The gel thus formed very quickly within 7.5 min [36]. Thiolated-peptides are also reported to cross-link methacrylated hyaluronic acid using the same chemistry, although the gelation time was more than 30 min [37].

Polyesters and polyamide-based hydrogels can be developed by condensation reaction resulting from the interaction between –OH groups or $–NH_2$ with –COOH, respectively. A highly efficient reagent for cross-linking hydrophilic polymers having amide groups is *N*,*N*-(3-dimethylaminopropyl)-*N*-ethyl carbodiimide (EDC). Gelatin hydrogels were reported to develop by EDC. In the Fig. 2, hydrogel matrix developed by physical and chemical cross-linking is displayed.

3.3 Mechanisms Affecting Hydrogels Biodegradation [39]

Biodegradation is a decisive requirement for the successful application of hydrogel in the field of controlled drug delivery and also to negate its surgical removal from the body. The controlled biodegradation can be materialized by the introduction of certain labile linkages such as esters, anhydrides, imine (Schiff bases), acetal, hemiacetal, ether, nitrile, phosphonate, polycyanoacrylate, and enzymaticaly labile peptides. Biodegradation leads to morphological deterioration evident from destroyed

crystallinity and molecular weight of the polymer. Eventually the physical properties are altered into a product of lower mechanical strength with less complex innocuous products which are easily eliminated from the body. Biodegradation mechanisms unveil the degradation products and the factors affecting this process. Biodegradation mechanisms can be classified into four different types: solubilization; ionization resulting in dissolution; chemical hydrolysis, and enzymatic degradation.

3.3.1 Solubilization

Hydrophilic polymer hydrogels are susceptible to degrade in-vivo by the water activity. Water diffuses inside the hydrogel matrix and transforms it into a swelled structure which ultimately solubilizes upon further uptake of water. Here, hydration of the polymer is a vital factor which again depends on the hydrophilicity of the polymer. Hydration is an indication of disruption of secondary and tertiary structures stabilized by van der Waals forces and hydrogen bonds. During the process of hydrogel swelling, water acts as plasticizer and the extent of swelling is balanced by the opposing forces of polymer-polymer interaction and polymer-water interaction. Synthetic water soluble polymers like polyvinyl alcohol, polyvinylpyrrolidone, polyphosphazenes, polyphosphanates, and natural polymers like dextran, hyaluronic acid, etc., degrades following solubilization mechanism. Alteration in environmental triggers like pH, ionic strength, or temperature also has substantial impact on this mechanism.

3.3.2 Ionization Resulting in Dissolution

Initially water insoluble polymers become soluble by the ionization or protonation of their pendant groups. Such polyacidic or polybasic hydrogels are studied to control the release of cargo molecules triggered by the pH of site of action. Such ionization of the pendant group influenced by surrounding pH makes the polymer hydrophilic and soluble. The polyacids ionizes in alkaline pH and polybasic materials protonates in acidic environment, resulting in their dissolution. Cellulose acetate phthalate becomes water soluble at a pH $>$ 6, while poly (vinyl acetate phthalate) and hydroxylpropylmethyl cellulose phthalate polymers ionized at a lower pH.

3.3.3 Chemical Hydrolysis

Chemical hydrolysis is, perhaps, the most explained mechanism for the biodegradation of synthetic water insoluble polymers. Crystalline feature of these polymers account for their water insolubility. So, there should be sufficient hydrolytically susceptible linkage in the polymer structure and again these linkages should be reasonably hydrophilic for water activity. Poly(lactic acid); poly(glycolic acid); poly(lactide-co-glycolide); polycaprolactone; polydioxanones; polyhydroxybutyrate and polyhydroxyvalerate; polycarbonates; and polyphosphates are the synthetic polymers that biodegrade by this mechanism. Polyanhydrides and polyesters are the most known polymer class that biodegrade by this mechanism. Polyanhydrides hydrolyzed to produce carboxylic acids; and polyesters produces carboxylic acid and alcohol moieties. Subsequent ionization of such carboxylic acids makes them water soluble and biodegradable. Generally, these polymers are combined with hydrophilic counterparts to fabricate tailorable biodegradable system. Polyphosphazenes are

another class of versatile polymer hydrolyzed by this mechanism to yield less toxic compounds like ammonia and phosphates.

3.3.4 Enzymatic Hydrolysis

Enzyme catalyzed biodegradation is another very significant mechanism contribute to the bioconversion of complex polymers into less toxic innocuous products. An enzyme catalyzes a specific reaction or a series of reactions like oxidation, reduction, hydrolysis, esterification, and molecular inter-conversions. Enzymes are divided into six classes, namely, oxido-reductase, transferase, hydrolase, lyase, isomerase, and ligase. Hydrolases are a group of hydrolytic enzymes that catalyzes the hydrolysis of chemical bonds. This group delivers their hydrolytic activity on C–O, C–N, and C–C bonds. As a matter of fact, these bonds are relevant to glycosidic bond of polysaccharides and peptide bond of protein molecules. So, in turn this enzyme group degrades the polysaccharide or protein-natured polymers. Hydrolases that act on proteins are again divided into two groups, peptidase (exo-peptidase) and proteinase (endo-peptidase). The exo-peptidases, namely, aminopeptidases and carboxypeptidases catalyze the hydrolysis of amino-terminal and carboxy-terminal of polypeptide chain, respectively. The endo-peptidases catalyze the hydrolysis of peptide bonds within the polypeptide chain. Hence, the protein-based polymer hydrogels like gelatin, collagen, albumin, and fibrin biodegrade by enzymatic means. Glycoside hydrolases also known as glycosidases or glycosyl hydrolases assist in the hydrolysis of glycosidic bonds of polysaccharides. Cellulase hydrolyzes cellulose; β-amylase hydrolyzes starch into maltose; and lipase hydrolyzes poly(vinylacetate) at the ester linkage to yield oligomers with acid and alcohol group. Glycosidase are of three classes that hydrolyze *O*-glycosyl, *N*-glycosyl, or *S*-glycosyl bonds in a polysaccharide chain, of which *O*-glycosidase is the largest one. Different enzymes, namely, cellulase, pectinase, pepsin, papain, lipase, and chitotriosidase have been reported to hydrolyze chitosan in-vivo. So, the site specific delivery of cargo molecules can possibly be achieved depending on the type and nature of enzyme present in place.

Enzymes impart substrate specific activity. If there is any alteration in substrate structure, enzyme activity will decline. This property can be utilized to make structurally well-equipped polymers and hydrogels to control their biodegradation by enzyme attack. Conformational changes in the polymer structure may also be triggered by the environmental stimuli like pH, ionic strength, or temperature. The rate and extent of enzyme penetration inside the hydrogel matrix can also be a deciding factor for its biodegradation. Highly cross-linked gel network can impose steric hindrance to the enzyme penetration. All these factors warrant careful examination for the development of biodegradable hydrogel for controlled drug delivery.

3.4 Factors Affecting Hydrogels Biodegradation [39]

Biodegradation being the decisive requirement for the hydrogels successful application as a controlled drug delivery device, the factors which are closely related to this draws particular attention. All the biopolymers and the synthetic polymers like

aliphatic polyesters and polyanhydrides contain hydrolysable groups along the parent chain responsible for their biodegradation. It has also been observed that the polymer characteristics like molecular weight, morphology, size, chemical composition, structural configuration, etc. has substantial effect on biodegradation. Hence, the author has made an attempt to discuss these issues in this section.

3.4.1 Physical Factor

The *molecular weight* is an important factor for the biodegradation of the polymer because it determines many physical properties. Molecular weight is a function of degree of polymerization. Degree of polymerization increases with the increase in number of repeating monomer units. Higher degree of polymerization endows a polymer with greater mechanical strength and high molecular weight. These polymers are less prone to enzymatic biodegradation (exo and endo cleavage type), in comparison to the polymers of low molecular weight. High molecular weight (Mn $>$ 4000) polycaprolactone was found to degrade slowly by lipase enzyme (endo-cleavage type) in comparison to its low molecular weight version.

The presence of *low molecular weight compounds* like monomers, oligomers, solvents, initiators, and drugs in the polymer architecture contribute to speed up the biodegradation process. In case of heterogeneous degradation method, the electrostatic interaction between the drug (acidic, basic, or amphoteric nature) and the matrix can drastically affect the degradation rate. Such degradation is characterized by the alteration of natural acid-base equilibrium of the matrix made of carboxylic end groups. When acidic drugs are loaded in the matrix, faster hydrolysis of ester bond is expected. When a basic drug is in place, two effects can be observed: when the drug is in excess with respect to carboxylic end, it catalyzes the cleavage of ester bond or otherwise decrease the degradation rate.

Polymer *morphology* greatly influences the biodegradation process. Initially, the amorphous region of the polymer entertains the water influx resulting in random hydrolytic scission of the hydrolysable/ester bonds. When most of the amorphous regions are degraded, hydrolytic attack progresses within the crystalline domain. Due to the *microstructure* feature of the amorphous region, the molecules are randomly oriented resulting in a loosely packed material more susceptible to attack by reacting species or solvent.

The equivalent repeating units of synthetic polymers contribute to their crystalline property. Due to a different *microstructure* of the crystalline region, the molecules are densely oriented, making them difficult for the enzyme to access the hydrolysable groups. However, the synthetic polymers with long repeating units are less crystalline and susceptible for enzymatic biodegradation. For example, subtilisin, a non-specific protease enzyme capable of degrading a series of poly amide-urethane.

High order structures like glass transition temperature, melting temperature, etc. play vital roles in biodegradation process. The temperature at which polymers experience its transition from rubbery to rigid glassy state is called *glass transition temperature* (T_g). The temperature above which a polymer becomes flexible, elastic, and rubbery is called *melting temperature* (T_m). Amorphous polymers are less

crystalline and hence they do not have specific melting point. Below the T_g, amorphous polymers are hard and brittle. Any temperature above the T_m induces molecular motion resulting in a typical rubbery elastic material. At a constant force above the T_g, the polymer becomes leathery first and then rubbery with increasing temperature. This result into a visco-elastic deformation, i.e., the polymer begins to creep. However, above the T_m, the polymer become viscous and the viscosity goes on decreasing with increase in temperature. These networks exhibit homogenous degradation and qualify them as a preferred matrix for controlled drug delivery.

3.4.2 Chemical Factor

The *chemical structure* of the polymer unveils its biodegradation pathway. The protein-based polymers undergo biodegradation via the cleavage of peptide linkage by the proteolytic enzymes. Polysaccharide-based biopolymers undergo such biodegradation by the action of glycosidase enzyme. The lipid conjugated polymers undergo similar degradation by the activity of lipase enzyme.

The presence of *ionic groups* such as –OH, –CONH, $–CONH_2$, –COOH, $–SO_3H$, etc., along the polymer chain, account for its hydrophilicity. This hydrophilic nature allow the water inside the polymer followed by its solubilization which ultimately determines the rate of hydrolysis and the type whether surface or bulk hydrolysis will take place. In cases when acidic or basic moieties are the by-products of polymeric breakdown, autocatalysis takes place.

Initially *hydrophobic* synthetic polymers possessing hydrolysable groups (in case of polyanhydrides and polyesters) undergo hydrolysis by water activity. Certain synthetic polymers biodegrade by enzymatic intervention must be supple enough to fit into the active site of the enzyme. The suppleness of aliphatic polyesters in comparison to the rigid aromatic poly(ethylene terephthalate) calls for its rapid biodegradation by enzyme activity. Here, the biodegradation is primarily attributed to the enzyme-substrate structural specificity. Henceforth, any structural alteration of the substrate will be reasoned for the failure of enzymatic degradation. High *cross-linking density* of the matrix is another reason that impedes the enzyme penetration resulting in slower biodegradation. The in accessibility of the enzyme to the substrate is primarily responsible for such slow process.

4 Strategies to Extend the Effectiveness of Hydrogel for Drug Delivery Application

4.1 Hydrogel-Drug Interactions [40, 41]

To extend the effectiveness of a hydrogel as a drug carrier involves many strategies. The hydrogel-drug interaction is one such important strategy. The drug pay load in the hydrogel can be accomplished by two approaches; post loading and in-situ loading. In post loading approach, the formed hydrogel is placed in the drug solution and the drug diffuses slowly inside the matrix due to the concentration gradient till equilibrium is attained. Physical interactions are basically accountable for the drug

pay load in this approach. In case of in-situ pay loading, a drug-polymer conjugate is developed which simultaneously gets encapsulated in course of hydrogel formation. Chemical interactions are primarily responsible for this kind of pay load approach. So, both physical and chemical interactions can be employed to enhance the drug binding in the hydrogel matrix and to extend the extent of drug release.

4.1.1 Physical Interactions

Ionic interactions are mostly employed to strengthen drug-hydrogel binding. The electrostatic attraction between the oppositely charged ions results into an ionic bond. Such bonds can be utilized to prolong the release of in house drug molecules. Anion and cation functionalized carbohydrate-based polymers have significant effects on prolonging the release of oppositely charged drugs. A study employed carboxymethyl curdlan as a hydrophilic anionic carrier to wrap a cationic antineoplastic drug doxorubicin via electrostatic interaction.

The effectiveness of phosphate-functionalized polymers is primarily attributed to the multivalent anionic charge of the phosphate ion. A soft contact lens fabricated with such phosphate-functionalized polymer had reportedly bound a cationic drug, naphazoline in quantities directly proportional to the phosphate content. An extended release profile was endowed by amino acid-modified gelatin hydrogels containing cationic trypsin inhibitor protein. The extent of release was directly proportional to the strength of the charge interactions between the amino acid chain and the entrapped proteins. Hence, the release of anionic drugs from hydrogel matrix could be tailored by the dynamic involvement of cationic monomers/polymers precursors.

Hydrophobic and ionic monomers can be incorporated to construct a copolymerized hydrogel. Hydrophobic monomers restrict the water activity and swelling of hydrogels. On the contrary, ionic monomers encourage hydrogel swelling. This balancing act of hydrogel swelling could be explored for extended drug delivery. One example of such kind would be the utilization of monomers like 4-vinylpyridine and *N*-(3-aminopropyl) methacrylamide to engineer poly 2-hydroxyethyl methacrylate (pHEMA) hydrogel that show improved drug pay load and concomitant extended release pattern.

There are certain complicated methods available to incorporate drugs within the polymer network. One such method is *molecular imprinting* where the monomers are spatially arranged for the polymerization process so that the drug release could be controlled. Another approach is the utilization of cyclodextrin that contain internal *nanocavities* to trap drug molecules and to release it for extended period of time. Increasing the percentage of cross-linked monomers, the microstructure of a hydrogel could be modified. This type of modification may yield a second hydrogel network within a pre-polymerized hydrogel. Such architecture reduces drugs permeability from the hydrogel surface and prolongs the release behavior.

4.1.2 Chemical Interactions

Drugs conjugation covalently with the hydrogels matrix is an important manifestation of chemical interaction. Such interaction is very useful to prolong the release profile. The release is primarily controlled by the rate of chemical or enzymatic

cleavage of *polymer-drug linkage.* For example, the controlled release of antineoplastic drug daunomycin from the cross-linked poly(aldehyde guluronate) hydrogel was achieved by the hydrolytic cleavage of drug-polymer covalent linkage. Similar strategy was adopted for controlled delivery of antibiotics by covalently conjugating it with the pre-polymers. In a different approach, hydrolytic cleavage of *polymer backbone* was investigated to regulate drug release. For instance, nonsteroidal anti-inflammatory drugs (NSAIDs) were partially modified to methacrylate analogs and conjugated to methacrylic-functionalized dextran hydrogel. As the hydrogel degrades, the NSAIDs analogs start releasing and a colon specific delivery was attained. *Modification of cross-linkers* may be another option to extend the release profile. It is evident from the extended release of Paclitaxel from 4 days to 2 weeks after the carbon number of a sulfide-based cross-linker increased from 3 to 4.

Protein and peptides exhibit very short half-lives (minutes to hours) in plasma. So, their half-life extension is a challenging task. To address this issue, β-eliminative linkers that cleave at a slower rate have been suggested to increase the half-life. These linkers could be used to fabricate the hydrogel and also to bind drugs with it. The release of cargo molecules from such hydrogel will solely be dependent on the *scission* of these linkers. Similar type of study was conducted where proteins were tethered to a large pore hydrogel developed from two multi-arm PEG macromonomers using β-eliminative linkers. The said linker was also used to cross-link four arms of each macro-monomer to form Tetra-PEG hydrogel. In this architecture, both the cleavage rates can be tuned to coordinate drug release and hydrogel degradation.

4.2 Gel Network Engineering [42, 43]

It is a continual process of exploring novel concepts to control the drugs release from the hydrogel matrix. The endeavor to achieve the spatial and temporal release of medicaments from the biodegradable matrix, engineering of such carrier has gained considerable attention. Investigations are focused towards the modification of hydrogel microstructure, either through the development of full gel network or at the hydrogel surface. Modification of microstructure may be achieved by increasing the percent of cross-linked monomers. However, such highly cross-linked networks may exhibit very slow response towards the environmental stimuli and may own undesirable mechanical strength. However, interpenetrating networks, control of surface diffusion, and composite hydrogels are the most popular approaches for gel network engineering.

4.2.1 Interpenetration Networks (IPNs)

IPNs are intimate combination of two polymers, at least one of which is synthesized and/or cross-linked in the immediate presence of the other. This is typically done by immersing a pre-polymerized hydrogel into a solution of monomers and a polymerization initiator. An IPN is distinguished from the multi-polymer combinations like polymer blends, blocks, and grafts, in two ways: (i) an IPN swells but does not

dissolve in solvents; and (ii) the creep and flow are suppressed. The interlocked polymer structure of IPN is believed to ensure bulk stability and surface morphology. The main advantage of IPN-based hydrogels are their dense matrix which feature tougher mechanical strength, controllable swelling, and more efficient drug loading compared to their conventional counterparts. Drug loading is often performed in conjunction with the polymerization of the interpenetrating hydrogel phase. IPN pore size and surface chemistry can be optimized to tailor the release kinetics, interaction with surrounding tissues, and its mechanical strength. Such hydrogels can also response sensibly to the environmental fluctuation and restrict the equilibrium swelling as a function of elasticity and cross-linking density of the interpenetrating phases, and consequently controls the drug release. An investigation reported a pH sensitive IPN hydrogel which exhibited linear swelling profile following the abrupt pH change in the range of 2–7.4 in contrary to the traditional pH sensitive hydrogels. The IPN was composed of an aromatic azo group containing pH sensitive polymer and a hydrolysable copolymer *N*-(2-hydroxypropyl) methacrylamide-dimethacryloylhydroxylamine. The composition of the IPN was manipulated to optimize the equilibrium swelling, modulus of elasticity, and the degradation rate of copolymer network. The study gives the impression that the carrier is a suitable platform for oral drug delivery. In another study, a thermosensitive IPN was reported to release diclofenac in a regulated mode. The IPN was composed of lightly cross-linked chitosan-PNIPAM network. The matrix showed significant drug loading in comparison to the PNIPAM counterpart and also responded sharply to the temperature fluctuations attributed to the PNIPAM thus regulating drug release. IPN hydrogels sensitive to both temperature and pH fluctuations were also reported. The investigators incorporated polyaspartic acid as the pH sensitive polymer and PNIPAM being sensible to temperature fluctuations. The hydrogel exhibited much faster shrinking and swelling depending on the composition. Another attractive approach may be the in-situ development of IPN by the polymerization of semi-IPN to modulate the release of protein like macromolecule upon injection. A study entertains this approach where dextran-methacrylate was dispersed into the calcium alginate hydrogel to produce a semi-IPN which showed different rheological properties from those of calcium alginate hydrogel. This allows hypodermic injection of semi-IPN with ease. The UV curing of this semi-IPN cross-links the methacrylate moieties to form the IPN hydrogel. A biodegradable IPN film composed of chitosan and gelatin were reported for the delivery of anticancer drug, 5-fluorouracil (5-FU). The IPN was prepared by solvent casting method using glutaraldehyde as a cross-linking agent. The in-vitro studies carried in phosphate buffer of pH 7.4 at 37 °C showed that the release of 5-FU extended upto 12 h with increasing gelatin amount in the film. The release rate was showed to increase with increased drug payload in the film.

4.2.2 Semi-interpenetration Networks (Semi-IPNs)

Semi-interpenetrating network is composed of one linear polymer penetrating into the other cross-linked network without any chemical bonds between them. In absence of restricting interpenetrating elastic network, semi-IPNs can effectively

preserve rapid kinetic response towards pH or temperature fluctuations, while still provide the benefits of IPN like modified pore size and slow drug release. In a study, a linear cationic polymer allylammonium chloride was aligned into the acryl amide/acrylic acid copolymer hydrogel which imparted higher mechanical strength and pH dependent "on-off" swelling to control theophylline release. Interestingly, both the covalent and ionic bonds were made into play for this network formation. The covalent bonds maintained the 3D structure and the ionic bonds imparted the hydrogel with higher mechanical strength and pH responsive behavior. Another very important study reported a semi-IPN hydrogel functioning as a nano-reactor that produces and stabilizes silver nanoparticles of 3–5 nm size. In this hydrogel, polyvinylpyrrolidone (PVP) chains were physically dispersed throughout the polyacrylamide (PAA) hydrogel network. This hydrogel-nanosilver architecture was found to have promising antibacterial effect. Another semi-IPN hydrogel was reported to be loaded with silver nanoparticles via in-situ reduction of silver nitrate by trisodium citrate. The hydrogel was developed using gum arabic and cross-linked polyhydroxyethyl methacrylate (PHEMA), in presence of ammonium persulfate (APS) and *N*, *N*-methylene bisacrylamide (MBAA) as an initiator and cross-linking agent, respectively. The hydrogel-stabilized silver nanoparticles showed excellent antibacterial activity. A semi-IPN hydrogel with a pH responsive swelling "on-off" behavior was reported to be composed of aligned amine-functional PNIPAM into the calcium chloride cross-linked sodium alginate network. The FTIR spectra confirmed the polyelectrolyte complex formation resulting from the reaction between carboxyl group of alginate and amino group of modified PNIPAM. In a separate case, a semi-IPN hydrogel was developed to deliver amoxicillin and metronidazole antibiotics in the stomach to treat *Helicobacter pylori.* The hydrogel utilized polyethylene oxide (PEO) dispersion into the cross-linked chitosan. The hydrogel showed increased swelling in acidic pH due to the amine functional groups of chitosan. Another study reported a semi-IPN hydrogel capable of delivering 5-aminosalicylic acid in the colon. The entrapment efficiency of the hydrogel was 85%. The semi-IPN was composed of guar gum (GG) and poly methacrylic acid (PMA) and showed very interesting interactions involved in the drug release. The hydrogels minimal swelling in acidic pH was attributed to the complex hydrogen-bonded structure and maximal swelling in colon pH 7.4 was attributed to the electrostatic repulsion due to the ionization of carboxylic groups. Moreover, this hydrogel degrades in colon by enzymatic intervention caused by cecal bacteria. This translated the hydrogel to release minimum amount of drug at pH 2.2 and maximum at pH 7.4. The magnitude of degradation was reported to be dependent on cross-linking agent concentration and GG content. The versatility of semi-IPNs is very evident from an in-vitro study where such networks were utilized to deliver Bovine serum albumin at simulated intestinal environment. PVP being very promising thermosensitive polymer was used along with carboxymethylcellulose (CMC) to form this network. The swelling "on-off" response was a function of volume phase transition temperature (VPTT) which again depends on CMC content and pH of the medium. VPTT was observed in buffer solution of pH 1.2 but not in the alkaline medium.

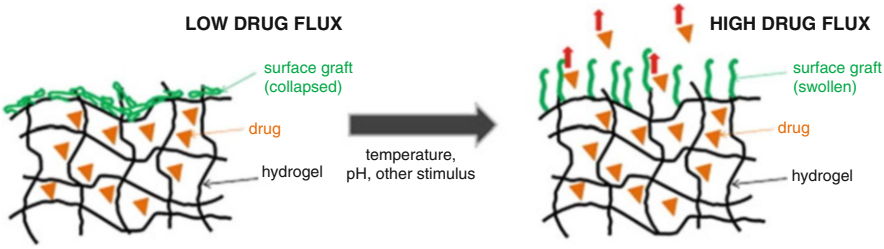


Fig. 3 Control of drug diffusion by surface modification of a hydrogel with environment responsive polymer graft. (Adopted from Ref. [43])

4.2.3 Surface Diffusion Control

An alternative strategy to linger drug release from the hydrogel is to perform surface-specific modifications. This is in contrary to the IPN where structural changes are made in the bulk of the hydrogel. In this approach, a film is generated around the hydrogel surface with reduced permeability. These types of films are often made in conjunction with a thermo-sensitive polymer like PNIPAM to exploit their temperature dependent "on-off" response for controlling drug release. Thermo-sensitive polymers exhibit a volume phase transition at certain temperature, which causes a sudden change in the solvation state. Polymers, which become insoluble upon heating, have a lower critical solution temperature (LCST) and those which become soluble upon heating have an upper critical solution temperature (UCST). PNIPAM exhibit LCST behavior with concomitant rapid drug release at lower temperature and slower drug release at higher temperature, because the polymer undergoes volume phase transition and collapses onto the hydrogel surface at higher temperature. An illustration of this mechanism is presented in Fig. 3. There are alternative strategies like coating a drug-loaded hydrogel with a dense polyelectrolyte multilayer film that restricts the drug diffusion out of the hydrogel bulk. The rate of drug diffusion will be dependent on the functionality of the multilayer film which again dependents on the pH of the medium, film degradation rate, and/or environmental triggers that control the swelling of the film.

4.2.4 Composite Hydrogel

Recently, microspheres, liposomes, and other multi-particulate drug delivery devices have gained significant popularity especially for achieving controlled release of orally administered drugs. They exhibit low risk of dose dumping, flexibility of blending to attain different release patterns, reproducible and short gastric residence time. As a result, interests are growing to develop composite hydrogels by entrapping the multi-particulate systems into the hydrogel matrix. This "carrier inside a carrier" concept not only avoids hydrogels limitations but also execute superior control over the drug release. Such a dual membrane concept to control drug release is illustrated in the Fig. 4. Biocompatibility of such composites supposed to remain uncompromised due to the distinct separation of the

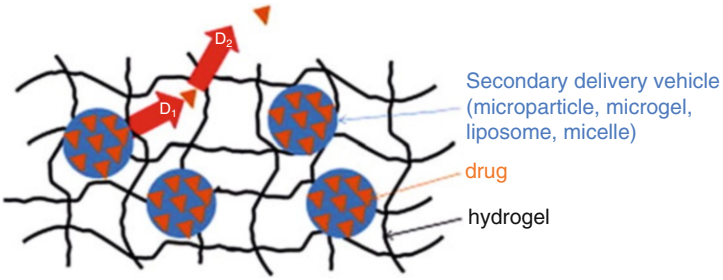


Fig. 4 A composite hydrogel containing drug encapsulated in a secondary controlled release vehicle (e.g., microparticles, nanoparticles, microgels, liposomes, micelles). D_1 and D_2 represent the diffusivity of drug (D_1 ¼ release from secondary release vehicle; D_2 ¼ diffusion through hydrogel). (Adopted from Ref. [43])

multiparticulate carriers from the hydrogel exterior. Moreover, this architecture may also prevent the migration of these microparticles away from their target site in-vivo. Poly(lactide-co-glycolide) (PLGA) nanoparticles when incorporated within a cross-linked hyaluronan-based hydrogel; the biocompatibility of the hydrogel remains uncompromised. Such composites improve the release kinetics rendered by microspheres by providing an additional diffusion barrier. This eliminates drugs burst release typically observed in microspheres. Physically cross-linked hydrogels are commonly employed to imbibe the multi-particulate carriers. In a study, PLGA microparticles were entrapped in a thermally reversible PNIPAM-g-chitosan hydrogel and the composite delivered 5-FU at nearly zero order with minimal burst effect. In another study, PLGA microparticles entrapped in polyvinyl alcohol (PVA) hydrogel exhibit nearly zero order release of dexamethasone for a period of 1 month. Liposomal vesicular carriers were entrapped in the hydrogel with the endeavor to prolong drug release. A study reports the loading of calcein and griseofulvin in liposome followed by its entrapment in carbopol 974 and hydroxyethylcellulose (HEC) hydrogel. The composite exhibited a delayed drug release. Another study reports liposomes entrapment in PHEMA hydrogels achieving controlled release of anti-glaucoma drugs for 8 days. Physically cross-linked hydrogels prepared in-situ could also be used to trap liposomes. One such composite has been reported where PNIPAM solution was mixed with NIPAM-octadecylacrylate copolymer functionalized liposomes at a temperature higher than 30 °C. This composite is equipped with thermosensitive and hydrophilic monomers exhibiting rapid drug release at a temperature higher than 30 °C.

Very interestingly, the release of different drugs from the same hydrogel could be accomplished by incorporating different copolymeric microgels loaded with drugs. For example, an NIPAM-*N*-tert-butylacrylamide (NIPAM-BAM) microgel can deliver pyrene while NIPAM-BAM-acrylic acid copolymer microgel can deliver rhodamine B at controllable rates. Surfactant stabilized micro-emulsion, surfactant micelles, and polymer micelles can similarly be entrapped in hydrogel networks to provide prolonged release. Polymeric micelles based on block

copolymers are very promising due to their low toxicity. For example, PNIPAM-block-poly(methyl methacrylate) micelles entrapped inside a PNIPAM hydrogel can release prednisone acetate in a controlled mode depending on the temperature of gel network.

5 Controlled Release Mechanisms of Hydrogels [44–47]

Hydrogels are engineered with unique characteristics to live the expectations of advanced drug delivery. Hydrogels engineered with hydrophilic polymers can imbibe large amount of water and therefore, the drug release mechanisms may vary from those hydrogels made with initially hydrophobic polymers. Both simple and sophisticated models have been developed to predict the release as a function of time. These models are based on the rate determining steps that control drug release and therefore categorized as below:

5.1 Diffusion Controlled System

Diffusion is the most widely applied mechanism to describe drug release from hydrogels. In diffusion controlled system, diffusion through a water insoluble barrier is the rate determining step. Hydrogels with pore sizes larger than drugs molecular size, diffusion coefficient is related to the porosity and tortuosity of the hydrogel. However, in case of nonporous and porous hydrogels with pore size comparable to the drugs molecular size, diffusion coefficient decreases due to the steric hindrance imparted by polymer chains within the cross-linked network. In such cases, the free space available for each drug molecule decreased and the hydrodynamic drag experienced by the drug is increased, leading to increased length of drug diffusion path. Diffusion controlled hydrogels are typically of reservoir and matrix/monolithic types. In both types of system, drugs are noncovalently embedded in the hydrogel matrices. Fick's laws of diffusion either with constant or variable diffusion coefficient or Stefan-Maxwell equations are commonly applied to describe diffusion from highly swollen hydrogel.

5.1.1 Reservoir Diffusion System

Reservoir type is one of the most common controlled drug delivery systems. In these systems, a drug core is coated with a hydrogel film and the rate of drug release is controlled by the properties of film (i.e., polymer composition and molecular weight); thickness of the film; and physicochemical properties of enclosed drug (i.e., solubility, particle size, and molecular weight). Reservoir systems are very useful for long-term site-specific delivery of drugs. On the basis of morphology, reservoir system can be spherical, cylindrical, or disc shaped.

In a reservoir system, the drug depot is surrounded by a polymer hydrogel film. To describe the drug release through the film, Fick's first law of diffusion can be used.

$$J_A = -D\frac{dC_A}{dx} \tag{1}$$

Here, J_A is molar flux or diffusion flux of the drug, i.e., amount of drug/area/time (mol/m^2/s), D is diffusion co-efficient, i.e., area/time (m^2/s) of the drug in the polymer, C_A is drug concentration, and X is the thickness of the film.

In a steady-state diffusion process, the molar flux and diffusion co-efficient of the drug remains constant, and the Eq. 1 can be integrated to give the following expression:

$$J_A = -K\frac{D\Delta C_A}{h} \tag{2}$$

Here, K is the partition co-efficient (ratio of drug concentration inside the hydrogel and outside solution of the hydrogel) and h is the hydrogel thickness.

For the constant drug release rate or flux from the reservoir, the concentration gradient should remain constant. This can be achieved by designing a device with excess solid drug in the core. Under these conditions, the internal solution in the core will remain saturated. This type of device is extremely useful for time-independent or zero-order release.

5.1.2 Matrix/Monolithic Diffusion System

In this system, drug is uniformly dispersed throughout the matrix and the drug release occurs at constant rate. Unlike the reservoir system, there is no danger of drug dumping in matrix system resulting due to accidental rupture of the film. However, the unsteady-state drug diffusion from one-dimensional *slab-shaped* matrix can be described by Fick's second law of diffusion:

$$\frac{dC_A}{dt} = D\frac{d^2C_A}{dx^2} \tag{3}$$

This equation can be rearranged to write the following expression:

$$\frac{dC_A}{dt} = \frac{d}{dx}\left(D\frac{dC_A}{dx}\right) \tag{4}$$

In this case, diffusion co-efficient is assumed to be constant. It is also assumed that sink conditions are maintained and the drug release from the thin *planar* geometric slab edge is neglected.

When diffusion co-efficient or diffusivity is concentration dependent, the following equation is used:

$$\frac{dC_A}{dt} = \frac{d}{dx}\left(DC_A\frac{dC_A}{dx}\right) \tag{5}$$

Many attempts modeled diffusion-controlled drug delivery from hydrogels to be largely dependent on the determination of diffusion co-efficient. Once the diffusion co-efficient is determined, Eqs. 1, 3, and 5 can be solved together with proper initial

and boundary conditions, to yield drug concentration profiles that dictate the release kinetics. For example, an exact analytical solution to Eq. 3 can be obtained using separation of variable technique. The ratio of the amount of drug released up to any time t (M_t) to the final amount of drug release (M_∞) can be expressed as:

$$\frac{M_t}{M_\infty} = 1 - \sum_{n=0}^{\infty} \frac{8}{(2n+1)^2 \pi^2} .\exp\left[\frac{-(2n+1)^2 A^2 Dt}{L^2}\right] \tag{6}$$

Once the appropriate diffusion co-efficient is obtained, the above equation can be used to predict the diffusion of small molecular weight drug and macromolecular proteins. Although such solution can be applied to different diffusion controlled system, model complexity is supposed to increase with the existence of nonspherical drugs and drug-polymer interactions.

Another empirical equation developed by Peppas assumed time-dependent power law function as below:

$$\frac{M_t}{M_\infty} = kt^n \tag{7}$$

Here, k is the geometric constant for a particular system and n is the release exponent representing release mechanism. The "n" values for different matrix geometry and release mechanism are listed in the Table 2.

It is important to note that in a purely swelling controlled planar geometric system, the release exponent equals to unity and hence, the fraction of drug release (M_t/M_∞) appears to follow zero order kinetics. This power law being simple can be applied to many diffusion controlled systems. However, the complicated release profiles may not be predicted precisely. For example, in diffusion controlled planar geometric system, the value of $n = 0.5$ and the power law is only valid for the first 60% release.

As the complexity of device geometry increases or in existence of variable drug diffusivity, Fick's laws may not be applied precisely. Table 3 represents the drug transport mechanisms for hydrogel slabs of planar geometry.

Diffusivity is a function of drug concentration and at the same time drugs diffusion from hydrogel matrix is also influenced by the degree of swelling and cross-linking density of the matrix. Therefore, the diffusion co-efficient used to describe drug release will be dependent on the fluctuations of environmental triggers and/or the bio-degradation of polymer network. The Fig. 5 makes an attempt to display the pictorial representation of matrix and reservoir system responsible for controlled drug delivery.

Table 2 Release exponent values (n) in the empirical power law model

Matrix geometry	Diffusion controlled system (Case I)	Swelling controlled system (Case II)
Planar	$n = 0.5$	$n = 1.0$
Cylinder	$n = 0.45$	$n = 0.89$
Sphere	$n = 0.43$	$n = 0.85$

Table 3 Drug transport mechanisms and diffusional exponents for hydrogel slab of planar geometry

Type of transport	Diffusional exponent (n)	Time dependence
Fickian diffusion	0.5	$t^{1/2}$
Anomalous transport	$0.5 < n < 1$	t^{n-1}
Case II transport	1	Time independent
Super case II transport	$n > 1$	t^{n-1}

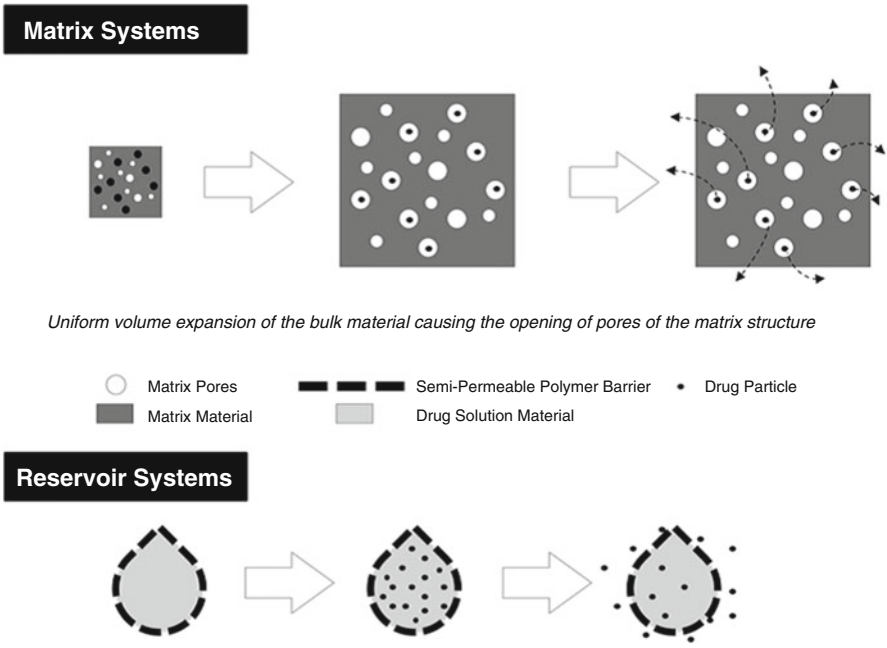


Fig. 5 Matrix and reservoir type hydrogels for controlled drug delivery

5.2 Swelling Controlled System

Swelling controlled system is a special type of solvent-activated system which delivers the low molecular weight drugs in a swelling controlled mode. The system is made by cross-linking hydrophilic macromolecules to form a three-dimensional network. The mechanism involving such system describes a moving boundary at the glassy and rubbery interface of swollen hydrogel where the drug molecules are released as illustrated in Fig. 6. These hydrogels impregnated with immobilized drugs undergo swelling driven phase transition from a glassy state to a rubbery state

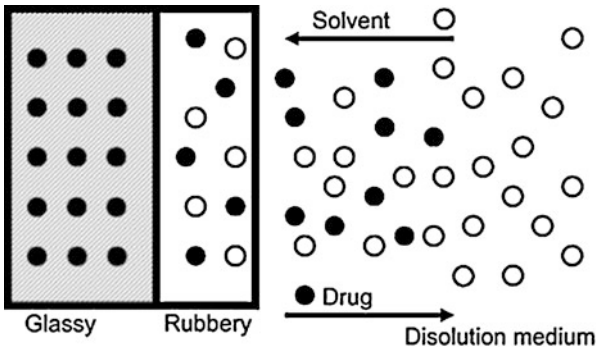


Fig. 6 Moving boundary at glassy and rubbery interface where drugs are released

and the drug molecules diffuse rapidly. This implies that the rate of drug release depends on rate of hydrogel swelling.

In this context, the swelling controlled drug release from hydroxypropyl methylcellulose (HPMC) tablet can be explained. HPMC tablet is a 3D hydrophilic matrix preserved in a dry glassy state. After oral administration, the tablet absorbs gastric fluid and a rapid transition from glassy to rubbery state takes place, once the T_g is reached. This results into an orderly release of the drug. In this case, two factors controlled the rate of drug release: (i) rate of water transport and (ii) gel layer thickness.

Drug release from polymer matrices can be estimated by two important parameters (i) drug diffusion time and (ii) polymer chain relaxation time. In case of diffusion controlled system, drug diffusion time (t) (where $t = \delta(t)^2/D$, here, $\delta(t)$ is the thickness of swelled phase at a particular time) is the rate-limiting step. While in case of swelling controlled system, polymer chain relaxation time (λ) is the rate-limiting step. The Deborah number (D_e) is used to compare these two time-scales:

$$D_e = \frac{\lambda}{t} = \frac{\lambda D}{\delta(t)^2} \tag{8}$$

In diffusion controlled system, $D_e \ll 1$; and Fickian diffusion dominates and the equations described in the previous section can be used to predict drug release. In swelling controlled system, $D_e \gg 1$; and the swelling rate of polymer network dictates the drug release rate.

The empirical power law (Eq. 7) which is used to describe diffusion controlled release from hydrogel matrices can also be used to describe swelling controlled release. A modification of Eq. 7 takes into account both the drug diffusion and polymer chain relaxation, as follows:

$$\frac{M_t}{M_\infty} = k_1 t^m + k_2 t^{2m} \tag{9}$$

Here, k_1, k_2, and m are constants. The two terms on the right side of the equation are diffusion and polymer chain relaxation's contribution to the release profile, respectively.

The above equation does not account for "moving boundary" concept, in which the gel swells heterogeneously as water penetrates. To describe such a system more precisely, Korsmeyer-Peppas introduced a dimensionless swelling interface number, S_w to correlate the "moving boundary" concept to hydrogel swelling:

$$S_w = \frac{V\delta(t)}{D} \tag{10}$$

Here, V is the velocity of hydrogel swelling front and D is the drugs diffusion co-efficient in the swollen phase. For a planar geometric system, when $S_w \ll 1$; the drug diffusion is much faster than the glassy rubbery interface movement and thus a zero-order release is expected.

Siepmann-Peppas developed a more rigorous method for predicting drug release from swelling controlled system based on sequential layer model. In this model, drug diffusion and polymer chain relaxation and dissolution, all are taken into account. Drug transport in both the radial and axial direction is accounted for using Fick's second law of diffusion in a cylindrical geometry with concentration dependent diffusion co-efficient:

$$\frac{dC_k}{dt} = \frac{d}{dr}\left(D_k \frac{dC_k}{dr}\right) + \frac{D_k}{r}\frac{dC_k}{dr} + \frac{d}{dz}\left(D_k \frac{dC_k}{dz}\right) \tag{11}$$

Here, C_k and D_k are the concentration and diffusivity of the diffusible species (water and drug), respectively. Concentration dependent diffusivities derived by a "Fujita-like" free-volume model expressed as follows:

$$D_1 = D_{1eq}\exp\left\{-\beta_1\left(1 - \frac{C_1}{C_{1eq}}\right)\right\} \tag{12}$$

$$D_2 = D_{2eq}\exp\left\{-\beta_2\left(1 - \frac{C_1}{C_{1eq}}\right)\right\} \tag{13}$$

Here, β_1 and β_2 are dimensionless constants and "eq" represents the equilibrium drug concentration at the water/matrix interface where polymer chain disentanglement occurs. Due to concentration dependent diffusivities, Eqs. 11, 12, and 13 can only be solved numerically. Siepmann and co-workers demonstrated that these numerical solutions corroborated well with experimental results. This model is therefore useful to predict the shape and dimensions of HPMC tablet needed to achieve desired release profile.

Based on Siepmann-Peppas work, Wu and co-workers [48] recently developed a mathematical model to describe swelling controlled release. Investigators introduced additional boundary conditions resulting from volume balance and accounted for two-dimensional movement of swelling front, in radial and axial directions. A tablet model was suggested assuming homogeneous drug-polymer mixture at zero time; perfect sink condition; and geometrical symmetry of the tablet. Model predictions

were again verified by compressed hydrogels tablets of polyethylene oxide (PEO). Water uptake, swelling, and dissolution behavior of PEO matrix controlled the drug release and corroborated well with the said mathematical model.

5.3 Chemically Controlled System

Chemically controlled systems refer to those systems whose drug release is dictated by the degradation reactions occurring within the delivery matrix. Such systems are classified into two major types, (i) the *pendant chain* system where polymer degradation (bond cleavage) is the rate determining step for the drug release, and diffusion is assumed to be negligible; and (ii) the *erodible drug delivery* system, where both the polymer degradation and drug diffusion occurs simultaneously. Hence, both the factors must be considered to predict the drug release precisely. The erodible systems are particularly fascinating when synthetic hydrogel systems are concerned. However, in both type of chemically controlled systems, diffusion does not determine the rate of drug release.

5.3.1 Pendant Chain System

The *pendant chain system* is one in which the drug molecule is chemically linked with biodegradable polymer backbone. The cleavage rate of such labile drug-polymer linkages in-vivo by chemical or enzymatic hydrolysis controls the drug release rate. Pendant chain systems are designed to enhance the therapeutic outcome of drugs. A classic example of such strategy is the delivery of growth factors which are mostly susceptible to proteolytic degradation. In such system, a fairly first order kinetic relationship can be observed between degradation rate of drug-polymer linkage and drug release rate. However, in cases when hydrogels are specifically designed to achieve targeted drug delivery, enzymatically cleavable spacer bonds may be incorporated. Hence, the bond cleavage kinetics, hydrogel microstructure, and the nature of degradation products are very important parameters which warrant considerable attention for developing hydrogel of this stature.

One example of fibrin matrix tied with pendant vascular endothelial growth factor (VEGF) is discussed here to describe the pendant chain system. The growth factor was covalently linked to the matrix by plasmin-sensitive [49] peptidyl substrate. The release of VEGF from such insoluble matrix will solely be controlled by plasmin-mediated cleavage of peptide substrate. A first-order cleavage kinetic was used to predict the time-dependent VEGF release. For more precise prediction of VEGF release, a description of VEGF release via matrix mediated degradation is required. Two adjustable parameters were therefore used to predict the VEGF release accurately. The first parameter was the pseudo first-order degradation rate constant. Both type of bond degradation (i) within fibrin network and (ii) the plasmin sensitive substrate that link VEGF to the fibrin matrix, were assumed to follow first order kinetics. The second parameter is the number of fibrin repeated units present between two cross-links. Pendant chain systems were occasionally designed to attain controlled release which may not be possible with diffusion controlled systems.

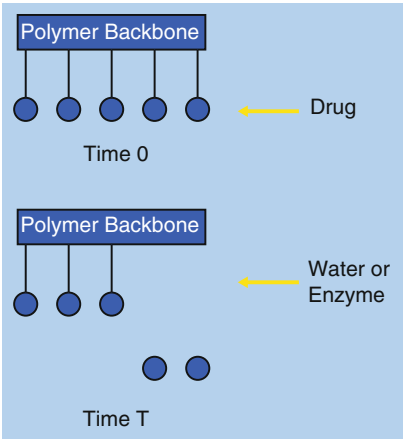


Fig. 7 Pendant chain system where the drug is chemically bonded with polymer backbone

Dubose and co-workers reported [50] covalently linked fluorescent-labeled probe molecules to the PEG-based hydrogel via step growth polymerization. Investigators demonstrated hydrolytic cleavage of covalent bonds, one within the cross-linked PEG network and the other associated with the immobilized probe molecules, resulting in a biphasic release profile. The first phase prior to hydrogel dissolution exhibits a constant drug release, and the second phase following hydrogel dissolution exhibits an almost instantaneous burst release. The authors demonstrated that the zero order delivery and the extent of burst release could be manipulated by cross-linker functionality (tetra-functional vs. octa-functional PEG) and degradation kinetics. The degradation behavior of certain bonds like amide, oxime, carboxylic ester, hydrazone, etc. depends on the pH, temperature, or bonds chemistry itself. Fig. 7 represents the pendant chain system where the drug is shown to be chemically bonded with polymer backbone and released by water or enzyme activity.

5.3.2 Erodible or Biodegradable System

In bio-erodible system, a controlled drug release is mediated through the concomitant erosion/degradation of the polymer network. The drug homogeneously dispersed in the polymer matrix will release slowly as the polymer disintegrates. The erosion depends on certain processes like degradation, dissolution, and diffusion. Thanks to the erodible systems for their two unique advantages: (i) polymers need not to be removed from the body after the drug exhaust and (ii) the drug need not to be water soluble. The erodible systems are of two types, namely, *surface erodible system* and *bulk erodible system*. Such a system is illustrated in the Fig. 8.

Surface Erodible System

In this system, the drug release is mediated by the surface erosion of polymer network. Surface erosion occurs when the rate of water penetration into the polymer matrix is much slower than the rate of bond hydrolysis. Hydrophobic polymer such as polyanhydrides and polyorthoesters exhibit this type of degradation behavior.

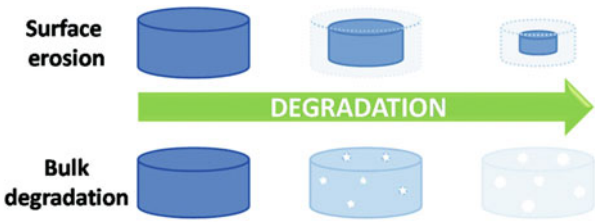


Fig. 8 Degradation mechanisms; surface erosion versus bulk degradation

However, the intrinsic character of hydrogel endows them with high water content for which surface erosion may primarily be attributed to the enzymatic hydrolysis. In such system, the enzyme penetration inside the hydrogel is much slower than the rate of enzymatic degradation. Rice and co-workers [51] illustrated surface erosion by enzymatic intervention. They studied the polyethylene glycol-polycaprolactone (PCL-PEG-PCL) block copolymer matrix erosion in presence of lipase enzyme. The advantage of surface eroding matrix is their structural integrity during drug release and a possibility to attain zero-order drug release by choosing suitable matrix geometry.

Hopfenberg developed one of the earliest mathematical models to describe the drug release from surface eroding matrix based on the matrix erosion rate. Equation 14 describes K_a as erosion rate constant, a_0 as initial dimension of delivery matrix (radius for spherical or cylindrical geometry and half thickness for planar geometry), and C_0 as initial drug concentration in the polymer matrix.

$$\frac{M_t}{M_\infty} = 1 - \left(1 - \frac{K_a t}{C_0 a_0}\right)^n \tag{14}$$

In this equation, "n" is a geometric factor and the value of 1, 2, and 3 represents planar, cylinder, and sphere geometry, respectively. In case of planar geometric matrix, $n = 1$, and drug release follows zero-order profile. Based on Hopfenberg's work, Katzhendler, Hoffman, and co-workers further developed a mathematical model for heterogeneous eroding networks. In this model, the swelling of polymer matrix was assumed to be slower than its erosion. It was adopted for hydrogel flat tablets with different rates of erosion in the radial and vertical direction. The kinetics of drug release from erodible polymer matrix with two co-ordinates "a" in radial and "b" in vertical directions can be described by the following equation:

$$\frac{M_t}{M_\infty} = 1 - \left(1 - \frac{K_a t}{C_0 a_0}\right)^2 \left(1 - \frac{2K_b t}{C_0 b_0}\right) \tag{15}$$

Here, a_0 and b_0 are the initial radius and thickness of the tablet, respectively. k_a and k_b are the radial and vertical erosion rate constant, respectively. Specific rates of drug delivery could be attained by changing the radius to thickness ratio of the matrix. It is worthy to note that this model does not takes into account the matrix swelling or assume it to occur prior to erosion and drug release.

Bulk Erodible System

In this system, the drug release is governed by bulk erosion of the polymer network and molecule diffusion. Bulk erosion occurs when the rate of water penetration inside the polymer matrix is much faster than the rate of polymer degradation. It implies that the whole system rapidly hydrates and the polymer chains break off throughout resulting in erosion happening in the entire system, i.e., a homogeneous process. Polymers like polylactic acid, polyglycolic acid, poly(lactide-co-glycolide), polycaprolactone, etc. exhibit this type of degradation behavior. A typical poly (lactide-co-glycolide) (PLGA) microspheres degrade by bulk erosion method. Different model are there to predict drug release and most of them takes into account either of the mechanisms like diffusion, swelling, or degradation. To meet the contemporary challenges, drug delivery devices are engineered which may not be explained simply by one mechanism. Same thing is applicable for bulk erodible systems where the drug release is governed by both network degradation and drug diffusion. Both the *degradation and diffusion* reactions are attributed to the swelling and mechanical phenomena of the network. The hydrolytic and enzymatic degradation of labile linkages of hydrogel can be tailored by various means. It has been observed that decrease in molecular diffusivity is proportional to the increase in cross-linking density, increase in molecular size, and increase in polymer volume fraction of the hydrogel. Sawhney developed a PLA-PEG-PLA block copolymer hydrogel using hydrophilic PEG macromer and PLA, a degradable moiety. The resulting hydrogel was susceptible to hydrolytic degradation, and the molecule diffusivity can be correlated with hydrogel degradation kinetics.

Heller and Baker developed a mathematical model to predict the drug release from initially water insoluble polymer matrix that hydrolytically converts to water soluble molecules. The model assumes the degradation of bulk eroding polymer following first-order kinetics. Heller and Baker modified the classical Higuchi equation as shown below [52]:

$$\frac{M_t}{A} = \sqrt{D(2C_0 - C_s)C_s t} \tag{16}$$

Here, $C_0 \gg C_s$ and M_t is the cumulative absolute amount of drug released at time t; A is the surface area of the controlled release device exposed to the release medium; D is the drug diffusivity in the polymer; C_0 is the initial drug concentration; and C_s is the drug solubility in the polymer.

They assumed that the drugs permeability in the biodegradable matrix is not constant and increases with time. In model, they applied the following ratio of drug permeability at time t (P_t) to the initial permeability (P_0):

$$\frac{P_t}{P_0} = \frac{\text{Initial number of Bonds}}{\text{Remaining number of Bonds}} = \frac{N}{N - Z}$$

where, N is the initial number of bonds and Z is the number of cleavage during time interval [0, t].

Polymer bonds are cleaved with the first order kinetics as follows:

$$\frac{dz}{dt} = K\,(N - Z) \tag{17}$$

where, K is the first-order rate constant.

After integration and rearrangement of Eq. 17, the following equation is obtained. This equation describes the drug release from thin slab with initial drug concentration above the drug solubility in hydrogel:

$$\frac{dM_t}{dt} = \frac{A}{2}\sqrt{\frac{2P_0 \exp(kt) C_0}{t}} \tag{18}$$

Charlier and co-workers [53] described another mathematical model to predict drug release from bulk eroding polymer film. They studied the mifepristone release from PLGA film matrix. Researcher assumed that the polymer degradation and drug diffusion are simultaneous process. They assumed a pseudo steady state, similar to Higuchi's classical equation (Eq. 16). Moreover, the model assumes the polymer chain to undergo first-order kinetics of cleavage and drug diffusion co-efficient is exponential functions of time:

$$D = D_0 \exp(kt) \tag{19}$$

In this equation, D_0 is the drug diffusion co-efficient at time $t = 0$, and k is the polymer degradation rate.

They got the following expression for the cumulative amount of drug release as a function of time:

$$Q = S\sqrt{\frac{2C_0 C_s D_0 [\exp(kt) - 1]}{k}} \tag{20}$$

where, S is the surface area of film in contact with the liquid medium, C_0 is the initial drug concentration, and C_s is the solubility of drug in the polymer.

5.4 Environmentally Responsive System [54–56]

Biodegradable hydrogels responsive to the environmental triggers are known as environmentally responsive system. pH, temperature, and enzyme responsive hydrogels are studied extensively to achieve site-specific controlled drug delivery. Certain hydrogels deliver cargo molecules in response to specific molecules like glucose. Light sensitive, pressure responsive, and electro-sensitive hydrogels are also potential candidates as drug delivery device.

Temperature sensitive hydrogels are perhaps the most commonly studied class of environmentally sensitive polymer systems in the arena of drug delivery. These

polymers exhibit temperature-dependent phase transition behavior. Polymers with UCST show increased water solubility with rise in temperature, whereas polymers with LCST show decreased water solubility with rise in temperature. LCST featured polymer made hydrogels shrink with the rise in temperature above LCST. Such polymers possess moderate quantum of hydrophobic moieties or a combination of hydrophobic and hydrophilic moieties. If the polymers are too hydrophobic, it remains completely insoluble in water. At lower temperature, the hydrogen bond between water molecules and hydrophilic moieties of the polymer dominates, resulting in enhanced water solubility. However, at higher temperature, the hydrogen bond becomes weak and the inter-polymer chain association by hydrophobic interaction strengthens. The net result is shrinking of the hydrogels. The LCST can be manipulated by adjusting the ratio of hydrophilic and hydrophobic moieties to have desirable swelling "on-off" behavior. For instance, a copolymer hydrogel developed by hydrophobic PNIPAM in association with hydrophilic acrylic acid monomer exhibited temperature dependent "on-off" swelling. Copolymerization of NIPAM with another hydrophobic monomer butyl methacrylate produced a hydrogel with tailorable mechanical strength. Thermo-reversible hydrogels investigated for parenteral administration must be biodegradable. To add biodegradable property, the polypropylene oxide (PPO) segment of PEO-PPO-PEO block copolymer is often replaced by biodegradable polylactic acid. It is important to note that noncovalently cross-linked temperature sensitive hydrogels may undergo sol-gel phase transitions, instead of swelling-shrinking transitions.

pH sensitive hydrogels are composed of cross-linked polyelectrolytes. Such hydrogels exhibit "on-off" swelling behavior depending on the pH of surrounding environment. pH sensitive polymers contain acidic (e.g., Carboxylic and sulfonic acids) or basic (e.g., ammonium salts) pendant groups. These functional groups either accept or donate proton depending on the surrounding pH. The hydrogels containing acidic functional group ionizes at higher pH whereas the basic functional groups ionize at lower pH. Ionization of such hydrogel translates into a swelled structure with concomitant release of cargo molecules. In absence of favorable pH, the functional groups remains unionized resulting in a collapsed hydrogel and the drug release halts. This pH-dependent swelling "on-off" can be applied to achieve site-specific controlled drug delivery. Polyacrylic acid (PAA) being anionic, ionizes at higher pH and swell. On the contrary, poly(diethylaminoethyl methacrylate) (PDEAEM) being cationic, ionized at lower pH and swell. This phenomenon is supported by a study conducted to evaluate the release behavior of caffeine from methyl methacrylate (MMA) and dimethylaminoethylmethacrylate (DMAEM) cationic hydrogel. The DMAEM monomer ionizes and swells at pH 3–5 and released caffeine at zero order.

When a small amount of anionic monomer (e.g., acrylic acid) is incorporated in a thermoreversible polymer, interestingly the LCST of the hydrogel shifts to the higher temperature. This is attributed to the ionization of pendant carboxyl groups leading to increased hydrophilicity and charge repulsion. In addition to this, higher the pKa value of a functional group in comparison to the surrounding pH, the functional group remains unionized and vice versa.

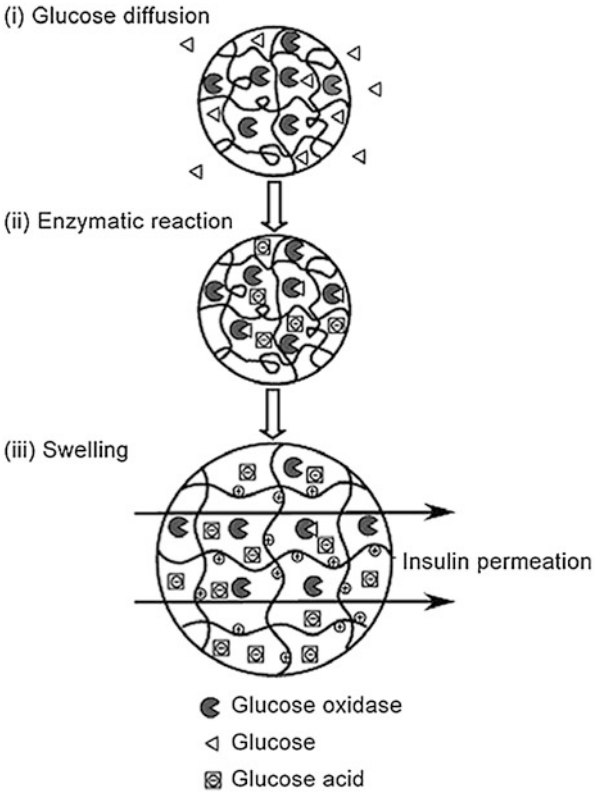


Fig. 9 Schematic representation of the glucose sensitive polyamine hydrogel loaded with enzyme glucose oxidase

Development of *self-regulated* insulin delivery device is the most challenging task. Insulin delivery warrants specialized equipment to release the optimum quantity at correct time. Hence, the self-regulated insulin delivery may be equipped with glucose sensing ability. Such a system is illustrated in the Fig. 9, where the enzyme glucose oxidase is immobilized in a polymer matrix. As the glucose diffuses the matrix interior, the enzyme oxidizes glucose into gluconic acid, resulting in lowering of matrix environmental pH. In this state of affair, the basic functional group of the polymer chain protonates and translates into a swelled hydrogel enabling the insulin release. This system functions on the basis of exterior glucose concentration. Insulin releases as the glucose mounts up outside the hydrogel and lowers the glucose level resulting in high matrix pH which ultimately stops further insulin release.

Another approach is based on competitive binding behavior of concanavalin A (Con A), a glucose binding lactin, which can bind both glycosylated insulin (G-insulin) and glucose. G-insulin bound to Con A can be displaced in response to glucose stimuli, thus functioning as a self-regulating insulin delivery system.

Electro-sensitive hydrogels undergo shrinking and swelling in response to applied electric field. Like the pH sensitive hydrogels, these hydrogels are also made of

polyelectrolytes. Very interestingly, these hydrogels show swelling on one side and shrinking on the other side, resulting in hydrogel bending. An investigation was reported that evaluated chitosan gels as electrically modulated drug delivery matrix. The release of neutral (hydrocortisone), anionic (benzoic acid), and cationic (lidocaine hydrochloride) drugs from the said hydrogel was monitored in response to different milli ampere current as a function of time. Similarly, chondroitin 4-sulfate hydrogels were evaluated as a potential matrix for electro-controlled delivery of peptides and proteins.

Light and *ion sensitive* hydrogels are elaborately described elsewhere and not included in this section.

6 Conclusions

Recently hydrogels have drawn considerable attention of the scientific fraternity for their unique features like tailorable hydrophilicity, environmental trigger-dependent "on-off" swelling, mechanical strength, and biocompatibility. They can be developed by wide array of methods using large number of precursors from natural, semi-synthetic, and synthetic origin. Their well-acceptable interaction with the cargo molecules have entertained their application in the field of controlled drug delivery. Biodegradable hydrogels are one step ahead of conventional hydrogels because such hydrogels bypass their surgical removal after the purpose is served. Moreover, the strategies involved in the development of biodegradable hydrogels offer superior control over the delivery of different-sized molecules in a temporal and spatial fashion. With all the added advantages, the applications of biodegradable hydrogels are supposed to increase in near future.

7 Future Scopes

The biggest advantage of biodegradable hydrogels is their in-vivo degradation behavior. The issue like residual accumulation of delivery device and the associated toxicity are adequately answered by such hydrogels. Physically or chemically derived hydrogels many a times avoid the use of high temperature or toxic organic solvent, which in turn beneficial for the labile or protein-natured drugs. Targeting a drug to a predetermined site can comfortably be achieved by designing biodegradable hydrogels responsive to the local triggers. The availability of wide-range natural and synthetic polymers equipped with cleavable linkages/bonds paved the way to develop hydrogels with suitable degradation in-vivo by water and enzyme activity. Various preparation methods are available that involves covalent and/or noncovalent forces. There are huge scopes to develop hydrogels of biodegradable nature by choosing suitable polymers, gelators, cross-linkers, preparation methods, etc. to meet the need of advanced drug delivery.

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Polysaccharide-*Aloe vera* Bioactive Hydrogels as Wound Care System

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Contents

Abstract

Wound care is an essential aspect of any trauma or surgical procedure. Designing an ideal wound healing system requires moist wound bed, proper exudate absorption, optimal diffusion of gases and minimum microbial invasion at the wound site which play a pivotal role. Therefore, choice of an ideal wound dressing is an essential step toward it contributing to the acceleration of wound repair and regeneration as well as prevention from microbial infection. This chapter is dedicated to the development of polysaccharide (PS)-based hydrogels for wound care system by incorporating herbal bioactive agents such as aloe vera which would provide deep insights into the designing aspect of the dressing by incorporation of features of the natural system. The healing aspect and tissue regeneration by PS or its combination with other natural polymers and aloe vera are discussed in the chapter.

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Aloe vera · Chitosan · Wound dressing · Hydrogel · Scar preventive

1 Introduction

The scientific world is looking for newer strategies and approaches to develop and design materials for wound repair and regeneration which provide an innovative therapeutic support to enhance the quality of human life. This is where the materials scientists, bioscientists, and medical fraternity have come together to bring out products with optimum bio-receptivity and performance at the site. Wound healing is a complex, step-by-step biological process that advances through a series of overlapping stages where numerous cellular components act together to regenerate the distorted tissue and maintain its integrity [1–4]. Several processes involving thrombogenesis, proliferation, angiogenesis, extracellular matrix (ECM) formation, and tissue remodeling take place at various stages of wound healing [5, 6]. Designing a wound healing system, key factors such as moist wound bed, proper exudate absorption, optimal diffusion of gases, and minimum microbial invasion at the wound site play a pivotal role [7, 8]. Negligence of the above factors can lead to chronic wounds. Excessive contact with exudate can lead to skin maceration and microbial proliferation, and it gives a foul smell with progressing days. Moreover, unassisted and prolonged wound healing causes scar formation. Therefore, the choice of an ideal wound dressing is an essential step contributing to the acceleration of wound repair and regeneration as well as prevention of microbial infection. Modern philosophy of wound care would require a procedure which would lead to healing without any histopathological complications. Thus, an ideal dressing is considered to be the one that stands up to the features, such as biocompatibility, biodegradability, antimicrobial nature, and superabsorbent nature with the scar prevention as displayed in Fig. 1.

Ancient methods of wound treatment utilized leaves of *Guiera senegalensis* (used in Senegal and Nigeria), barks of *Spathodea campanulata* and extracts of herbs and medicinal plants like *Commelina* which were applied directly to the skin [9]. However, it contained harmful components which often caused burning sensation and rashes, further becoming the source of infection. Growing awareness of clean and sterile medical practices helped in shifting to cotton-based gauze dressings that are being widely used till date. Their most acclaimed shortcoming was the painful dressing removal as it adhered to the tissue. Also, they lead to wound dehydration leading to cell desiccation [10].The shortcomings of gauze dressings elicited the revolution of hydrocolloid and hydrogel-based dressings. The ability of hydrogels to absorb greater volumes of exudate than their dry weight as well as the property of hydrocolloids to form a thick gel upon contact with exudate makes them indispensable for wound dressings. The most advantageous reason was the ability to provide a moist environment and painless removal of the dressing, a big relief for patients [11]. Numerous wound dressings in the form of

Fig. 1 Ideal requirements of a wound dressing

hydrogel gauzes have been designed, and few are commercially available. However, dressings that fulfill the absolute needs of an ideal wound care material require focused research.

Advanced dressings comprise of polymer-based films and foams that act as an interface with the surrounding environment, inhibit microbial invasion, and facilitate scar-free healing along with reepithelialization. Biopolymer-based materials, both synthetic and natural, have been the most promising bioresource for fabricating efficient wound care systems due to their biodegradability, biocompatibility, ease of solubility and fabrication, ease of immobilization of bioactive agents, cost-effectiveness, and inherent hydrophilicity in conjugation with a wide variety of chemical functionalities. Moreover, the malleability of such biopolymeric hydrogels with tunable surface and mechanical properties with other polymers or smaller antimicrobial molecules and agents by encapsulation or blending presents an economical and effective route [12].This has led to its extensive and elaborate research in the field of healthcare applications. Bioactive dressings in combination with synthetic and natural pharmacologically active agents are expected to accelerate wound healing with improved aesthetic appearance. The recent focus on the selective superiority of bio-based herbal agents in comparison with synthetic agents in regard to their multifunctionality, minimal toxicity, and ease of availability has facilitated its increased inclusion in wound dressings. Aloe vera has emerged to be an effective gel for wound healing applications promoting regeneration (elaborate discussion in a later section). The compounded effect of aloe vera's scar-free healing ability and the biocompatible and biodegradable matrix providing mechanical stability holds potential for wound care applications. Therefore, this chapter presents an elaborate discussion on polysaccharide and aloe vera based wound dressings.

2 Polysaccharides and Bioactive Moieties

Natural polymers are generally categorized as those obtained from natural sources and usually comprise of proteins or polysaccharides and represent a large domain of neutral (dextrans, glucans, cellulosic), basic (chitin, chitosan), acidic (alginic acid, hyaluronic acid, pectin), or sulfated polysaccharides (dermatan sulfate, keratan sulfate, heparin, chondroitin) for biomedical applications such as in dressings for burn patients. Moreover, polysaccharides form colloidal and hydrogel matrices that mimic the texture of living tissue when hydrated and offer the requisite mechanical strength in regard to the wear and tear of a dressing. Polysaccharides offer low immunogenicity, the minimal toxicity of degraded products, and induced healing effects making them ideal matrices for wound dressings [13, 14]. Advanced therapeutic dressings would need consideration of these very aspects of materials and bioactive components [15].The functionality of such materials can be boosted by combining different biopolymers to gain synergistic functional advantages over each of the pure components. Alginates and pectin have acquired a wide role in combination with aloe vera [16–18]. Recently, oxidized pectin–gelatin (OP–gel) matrices loaded with aloe vera were used as antimicrobial finishes on cotton gauzes to fabricate wound care devices. Aloe vera-loaded OP–gel dressings at 40% aloe vera content exhibited ∼84% antimicrobial activity against *Escherichia coli* (*E. coli*) as well as *Staphylococcus aureus* (*S. aureus*) evidenced by the colony-forming units (CFU) method. OP–gel–Aloe vera-treated wounds showed a very rapid healing with 80% of the healing in just 8 days with diminished scar formation as depicted in Fig. 2 [19]. The dressing was also evaluated for cytocompatibility using NIH3T3 mouse fibroblast cells, and the results revealed high viability with good cell attachment and proliferation [19].

These new devices not only exert mechanical protective function at the wound site but also act as a carrier for the release of various bioactive agents. Moreover, chitosan has gained unique attention within the world of polysaccharides due to its novel features such as reactive functionality, gel-forming ability, biodegradability, hemostatic nature, and high water absorption capacity along with antimicrobial behavior. The hydrogel nature helps in the diffusion of metabolites across the swollen matrix and hence makes it more adaptable to the biosystem.

A moist environment is one of the important stimulations to achieve faster healing considering the modern concept of wound care systems, and a remarkable mucoadhesive feature of the hydrogel in its swollen state facilitates adhesion in epithelial cells. This versatile combination of integral features within one single structure has generated enormous opportunities for chitosanin in the human healthcare system.

The advantage with polysaccharide is the offer of functional groups like hydroxyls and carbonyl groups that can be tailored chemically to bond with bioactive moieties like essential oils or therapeutic agents to fabricate composite dressings. The incorporation of bioactive moieties into polysaccharide matrices and its effectiveness as wound dressing have been evaluated in several studies [20, 21]. Herbal components such as aloe vera or essential oils like lavender oil, citrus

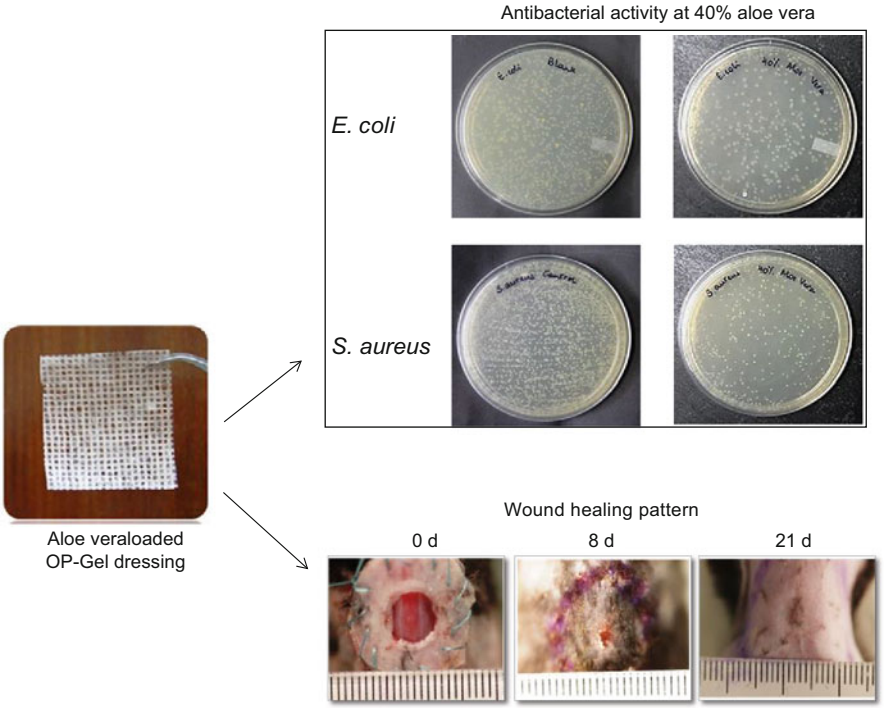

Fig. 2 Infection control and wound healing characteristics of aloe vera-loaded OP–gel wound dressings [19]

oil, sandalwood oil, and clove oil can be of great significance in improving patient's compliance and comfort [22, 23]. Numerous investigations have been dedicated to the design of chitosan matrix with herbal as well as nonherbal components. In the nonherbal studies, antibiotics and silver have been widely used. However, recent developments have been directed towards the herbal components with an aim to control the infection and have expedited healing at the wound site. Oregano essential oil loaded chitosan nanoparticles with size range of 40-80 nm were developed by a two-step method where the release behavior of essential oil was dependent on the concentration of various components in the system [24]. Similarly, Eugenol has been also incorporated into chitosan nanoparticles with an average size of less than 100 nm. Particles were thermally stable and can be utilized as antioxidants. In another study, thymol was loaded in zein nanoparticles stabilized with sodium caseinate and chitosan hydrochloride to fight against gram-positive bacterium [25]. Due to the hydrophobic nature of essential oils, there arises solubility issue which reduces their compatibility within the polymer system. Also, the monitoring of their release characteristics in biological fluids becomes difficult due to hydrophobicity. Therefore, aloe vera due to its remarkable hydrogel nature is being extensively used over other herbal bioactive components and is a motif of rising interest in the area of healthcare applications.

3 Aloe vera as Therapeutic Moiety

Traditional medicine from nature has been in practice for many centuries by a substantial proportion of the population. The plant's extracts may contain polysaccharides, proteins, or bioactive components and have been the main medicinal source for its curative and therapeutic properties against various infectious diseases. Aloe vera belongs to a cactus family and has been recognized as the source for diverse skin care products and medical formulations due to a wide range of active components as reviewed recently by Sànchez-Machado et al. [26]. Aloe vera has a beautiful combination of innovative features such as antimicrobial nature, anti-inflammatory action, antiaging effect, and antioxidant and anticancer behavior and has been recognized as a *wonder gel*. The antimicrobial effects of aloe vera have been attributed to specific plant components, such as anthraquinones, dihydroxyanthraquinones, and saponins. It generally contains aloe-emodin and aloin as the anthraquinones [27]. Aloe vera has been observed to be effective against both gram-negative and gram-positive microbes such as *E. coli*, *S. aureus*, and *K. pneumoniae* [28, 29]. Additionally, glycoproteins, gamma-linolenic acid, prostaglandins, and mucopolysaccharides are also responsible for its antibacterial properties, particularly against *S. aureus*. The product is so interesting that it has taken over the market in the food industry as drinks or as food supplement. The medicinal value the gel has immerged into the development of enormous cosmetic and medical products for human healthcare systems [30]. The versatility and multifaceted advantages of aloe vera have been incorporated in polymeric matrix so as to elicit those compounded properties into the matrix. Balaji et al. have reviewed biomaterial-based nano-applications of aloe vera in the broad spectrum of biomedical engineering [31]. The applications of aloe vera have been highlighted for three major areas in the biomedical field – wound healing, tissue engineering, and drug delivery. The presence of various components ranging from sugars, minerals, lipids, steroids, aloins, glycoproteins, enzymes, salicylic acid, hormones, to essential vitamins cater to its commendable features. Combing aloe vera with biopolymeric hydrogels and films amplifies the biocompatibility of aloe vera in tissue engineering applications by inducing faster wound healing, with protection against a wide spectrum of microbes followed by enhanced cell adhesion and differentiation. Wahedi et al. studied the effects of the major constituent, aloesin, from Aloe vera on cutaneous wound healing [32]. Their attempt of in-depth understanding on the mechanism involved using MAPK/Rho and Smad signaling pathways in vitro and in vivo animal models has given a new dimension to aloe vera being ideal for wound healing. An upregulation of MAPK and Smad signal proteins was a clear indication of enhanced cell migration, angiogenesis, and neo-tissue formation. It was corroborated by the increased expression of phosphorylated Cdc42 and Rac1 proteins along with the augmented, positively upregulated cytokines and growth factors like IL-1β, IL-6, TGF-β1, and TNF-α. The emergence of Aloe vera for wound healing can be understood from a recent study conducted using three species of Aloe vera and the chemical characterization of the gel material and whole leaf material using nuclear magnetic resonance spectroscopy [33].

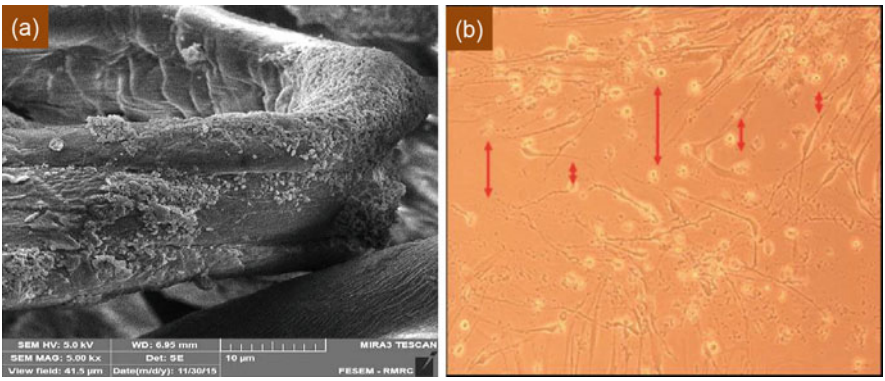

Fig. 3 (**a**) FESEM images of cotton fabric loaded with nanocapsules containing aloe vera extract and (**b**) cell migration in 24 h for treated cotton fabric [37]

While both gel and whole leaf material showed the presence of aloverose (partly acetylated polymannose/acemannan), glucose, malic acid, and a whole leaf marker, isocitric acid, were found exclusively in the leaf material. However, the gel showed better wound healing, cell migration, and wound closure.

Synthetic hydrogels such as polyvinyl pyrrolidone (PVP)/polyvinyl alcohol (PVA) in combination with aloe vera have been investigated for the wound care system. In a study, the copolymer of PVP and polyacrylamide has been used as the hydrogel matrix by in situ formation of the composite of aloe vera with the copolymer [34]. However, there has been extensive interest in the use of natural polymers in combination with synthetic ones or individually in this domain [35, 36]. Herbal wound dressings were prepared by coating tragacanth gum nanocapsules encapsulating aloe vera onto cotton fabric as observed under field emission scanning electron microscopy (FESEM) (Fig. 3a). Dressings exhibited good antimicrobial activity with 88% fibroblast cells migration in 24 h (Fig. 3b) [37]. Similarly, highly stable and flexible freeze-dried membranes were designed by incorporating aloe vera in varying weight ratios, i.e., 20%, 30%, 40%, and 50%, into PVA/polyethylene oxide/carboxymethyl cellulose (PVA/PEO/CMC) gel in ratio (80/20/20) to act as wound care membranes. Antibacterial activity of membranes was calculated using CFU method, and significant reduction in the bacterial number against *E.coli* was manifested with highest activity of 93.6% at 50% aloe vera content [38].

In spite of being a wonderful therapeutic agent, aloe vera is a mild antimicrobial agent and hence has limitations in controlling infection related to highly contaminated wounds. This is the reason that a combination of the aloe vera with strong antimicrobial agents such as nanosilver or antibiotics is sometimes required under chronic conditions. In this regard, PVA/PEO/CMC gel was further used in combination with nanosilver nanohydrogel (nSnH) of poly(methacrylic acid) (PMAA) prepared using emulsion technique with subsequent incorporation of aloe vera (at 10% concentration) as bioactive agent for the development of antimicrobial nanobiocomposite wound dressings [22]. Scanning electron microscopy (SEM)

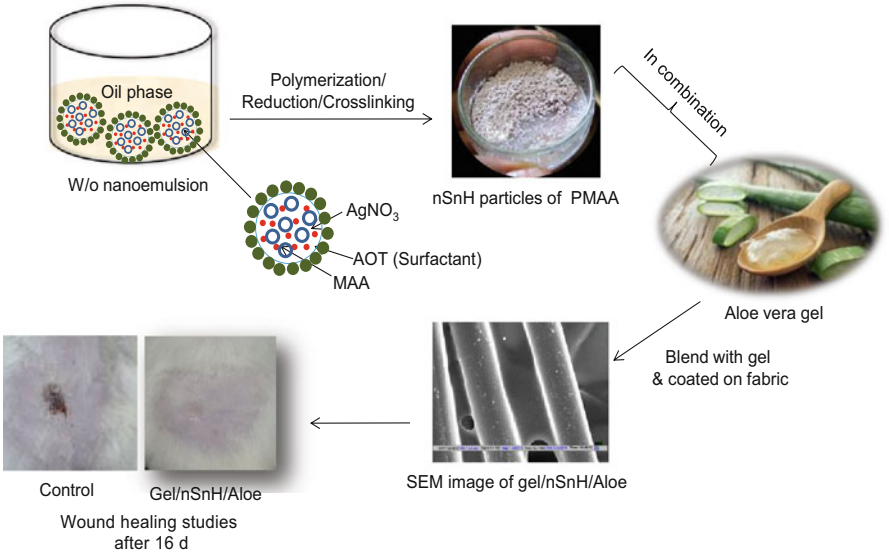

Fig. 4 Aloe vera incorporated with nSnH particles of PMAA showing excellent wound healing in 16 days [22]

results indicated the formation of a homogeneous blend. Antimicrobial results revealed that the presence of nSnH in dressings in conjugation with aloe vera enhanced antibacterial activity up to >98% against *E. coli* and *S. aureus* even at low aloe content, thus, notably minimizing the chances of infection at the site. Complete wound healing was observed post-16th day in gel/nSnH/Aloe vera dressings as depicted in Fig. 4.

Rapid healing can be ascribed to the cumulative effect of aloe vera and nSnH, where nSnH plays an excellent role in complete eradication of infection and aloe vera provides the moist environment at the wound surface leading to increased fibroblast proliferation, accelerated wound contraction, and faster rate of healing. Interestingly, the gel has occupied an integral place in the field of wound care systems to provide smooth healing. Exudating wounds provide a favorable environment for the bacterial invasion and proliferation which may lead to severe contamination and wound deterioration [39]. The long-lived ancient remedy of Aloe vera on burn wounds has been validated and reviewed by Maenthaisong et al. using 4 studies with 137 patients by collection of databases from various sources like MEDLINE, CINAHL, Cochrane Library, HealthStar, DARE, etc. [40]. They report this study to be the first systematic review on the efficacy of Aloe vera on highly exudating burn wounds. All comparative studies of aloe vera to commercially available Vaseline gauze, silver sulfadiazine cream, and framycetin cream have exhibited the superior healing efficiency of Aloe vera. In a study, the average healing time of wound with aloe vera was 6.3 days shorter as compared to the vaseline gauze along with higher rate of epithelialization, measured in terms of the healing size. Further, a success rate

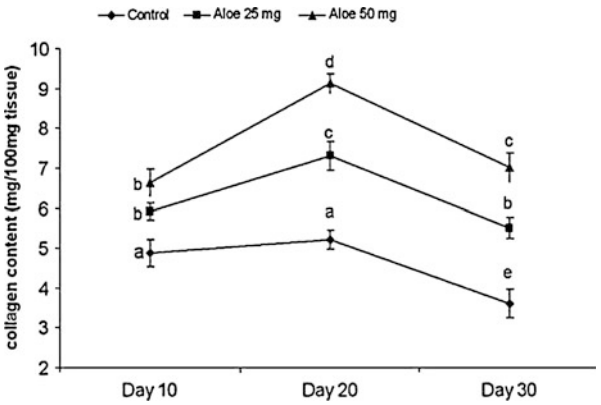

Fig. 5 Effect of topical application of different doses of aloe vera polysaccharide on collagen concentration at the 10th, 20th, and 30th day after wound creation. The different letters above each bar represent significant difference at $P < 0.05$ [46]

of 95% with aloe vera was noticed in comparison to sulfadiazine that displayed 83% during experiments on burn wounds. Apart from mild discomfort and transient pains counteracted by oral administration, Aloe vera was found to be safe in the studies. Reepithelialization with aloe vera was effective till second-degree wounds that was fostered by collagen synthesis, fibroblast stimulation, antimicrobial effect, and moisturizing effect. Here, aloe vera performs a proactive role by exerting its bioactive character [41]. Aloe vera contains huge potentially active constituents involving vitamins, enzymes, minerals, sugars, lignin, saponins, salicylic acid, and amino acids along with polysaccharides [42, 43]. Mannose-6-phosphate, a constituent of aloe, has been observed to contribute to faster wound healing and inflammation-reducing properties [44]. However; it is the synergistic effect of various constituents in aloe vera gel that is reflected in such diverse features of this material [45]. Similarly, glucomannan is the polysaccharide constituent in aloe vera which also helps in the wound healing process. It has been proposed that aloe vera contains a glycoprotein with cell proliferating activity that helps in angiogenesis. Studies have also demonstrated that aloe vera gel induces matrix metalloproteinases (MMPs) and tissue inhibitors of matrix metalloproteinase (TIMP) gene expression, and any alterations in their levels play an essential role in all aspects of wound repair and contraction [46].

MMP-3 is secreted by fibroblasts and its activity is important in regulating wound healing progression. Similarly, TIMP-2 accelerates keratinocyte migration in culture and in vivo. Aloe vera effectively maintains a balance between MMP and TIMP levels to promote cell migration and wound closure.

Also, it exerts a stimulatory effect to enhance the production of n-acetyl glucosamine (NAGA), n-acetyl galactosamine (NAGLA), and collagen contents (Fig. 5) as measured by standard biochemical methods, thus resulting in orderly deposition of structural matrix during wound repair.

A research group has developed sponges of aloe vera gel by freeze-drying process by using a thin layer of gellan gum for stabilizing the matrix [47]. The gel showed a heterogeneous but interconnected structure with a porosity of 72–77% with very high swelling of >3000% accompanied by good cytocompatibility [48]. By virtue of the presence of polysaccharide components in aloe vera extract, it can be easily

cross-linked by using calcium ions which bind the molecular chain by bridging carboxyl groups [49]. An excellent study by Rodriguez-Bigas was carried out by using aloe vera gel, silver sulfadiazine, and salicylic acid on full-thickness burn wounds in guinea pigs [50]. Aloe gel permitted a faster healing of burn wounds as compared to the other two components. Furthermore, aloe vera has been combined with antibiotics as well, such as amoxicillin or nystatin, to develop sponges which would provide strong bioactivity in a system. Interestingly, the gel has shown potential as a capping agent for antimicrobials like zinc oxide nanoparticles that have shown good antibacterial behavior against *E. coli*, *Pseudomonas aeruginosa* (*P. aeruginosa*), and methicillin-resistant *S. aureus* (MRSA) [51].

4 Chitosan–Aloe vera as the Wound Care Hydrogel

A large number of natural polymers have been investigated as hydrogels for a wide range of medical applications. However, chitosan is a well-known polysaccharide from a commercial point of view in wound management. To overcome the dual challenges of bleeding and contamination at the wound site, a chitosan-based dressing with improved hemostatic, antimicrobial, and scar-preventive properties is of great significance [52, 53]. The chemistry of chitosan involves a copolymer structure consisting of D-glucosamine units with a few *N*-acetyl, D-glucosamine units distributed along the molecular chain (Fig. 6). The focal point of attraction for many bioscientists is the amino group at C2 position which may be used either as such for the immobilization of bioactive components or may be transformed into another functionality to achieve desired biomaterial. The combination of the hydroxyl and amino groups within the structure makes the polymer useful for a large number of biomedical applications. The advantage of this polymer is that it is soluble in water under mild acidic pH ($\leq$6) due to protonation of amino groups which transforms it into cationic polyelectrolyte and hence can be formed into various shapes with ease. Moreover, the hydrogel is susceptible to degradation by lysozyme and hence has the advantage of biodegradation from the site of application in the human body.

Chitosan may be processed into different shapes of films, fibers, nanoparticles, and nanocomposites from an acidified aqueous system which makes it very attractive for biomedical applications. The beauty of chitosan as a molecule is that it helps in scar prevention probably by mimicking the hyaluronic structure in a system. The investigations on mice as the animal model have shown that scar formation is reduced to ~2% by using chitosan in combination with PVP and PEG [54]. This

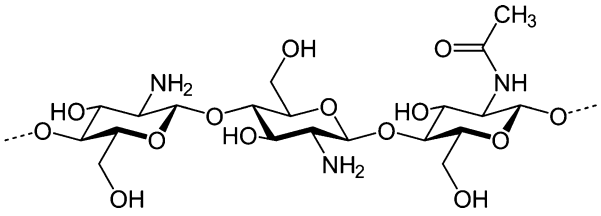

Fig. 6 Representation of the chemical structure of chitosan

is an interesting outcome and may lead to significant developments in chitosan-based products if used in combination with aloe vera. The development of a wound care system using this therapeutic amalgamation would be very advantageous toward the development of medical devices. A dressing with these features may be projected as one of the most interesting ones out of the one available today.

Enormous efforts have been made within the domain of a chitosan-based wound care system. Chitosan and native aloe vera gel combinations were explored as an approach to develop blended membranes for effective wound management. Both chitosan and aloe vera have such a mutual chemistry in wound care that both have been credited to be the two *gifts of nature* [55]. Menda et al. investigated chitosan–aloe system as film for antimicrobial wound care system and compared it with chitosan–calendula (*C. officinalis*) composition. Although the aloe-based system was good enough, a more precise investigation involving animal models would provide critical information on the relative efficacy of the two systems [56].The effect of aloe vera incorporation in chitosan films in regard to their water vapor permeability, color, and mechanical properties has been studied extensively by Khoshgozaran-Abras et al. [57]. The increased mechanical properties and a decrease in water vapor permeability were indicative of strong interaction between aloe vera and chitosan. This fact was validated by the decrease in water solubility with increased aloe vera content due to the increased interactions. They optimized incorporation till 20% to be ideal with suitable flexibility and toughness. A chitosan–aloe vera (CS/AV) membrane has been developed using glycerol as the plasticizer so that matrix acquires flexibility and handling becomes easier [58]. The CS/AV composition was confined to 2:1 and 1:1 ratios for investigating the antimicrobial nature as well as cell viability. The antimicrobial efficacy against *S. aureus* showed better control of the antibacterial nature in membranes with higher AV content. These membranes were observed to provide excellent surfaces for the attachment and proliferation of human dermal fibroblast cells which open up their application in wound care systems. Pereira et al. carried out an interesting piece of work by preparing the nano- and microparticles of chitosan and aloe vera in combination with vitamin E [59].The formulation was found to be very effective for skin burns. Particles were prepared by atomization of the solution and were dispersed into poloxamer gel. The composition provided superior healing as compared to the one without particles.

Certain studies have reported that cross-linking of chitosan plays an important role during applications for highly exudating wounds. Chitosan may be combined with polyethylene glycol (PEG) and PVP as the hydrogel component so that a superabsorbent matrix is created which would help in large exudate absorption from the wound. In a further development, the matrix may be freeze dried so that a porous morphology is created which would allow much higher exudate absorption from the wound due to a combined effect of capillary action and the hydrophilicity of the matrix [60]. However, it may become necessary to cross-link the matrix where large exudates are formed so that the matrix does not deform in an uncontrolled manner. The cross-linkers may be selected from within a large number of chemicals such as glyoxal, boric acid, genipin, and gamma radiation [61, 62]. This suggests

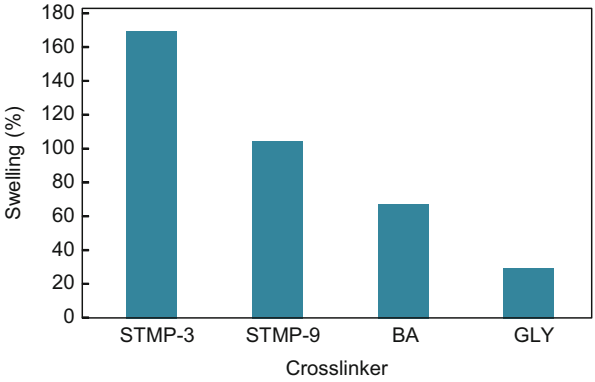

Fig. 7 Swelling variation with different cross-linkers represented as STMP, sodium trimetaphosphate at pH 3 and 9; BA, boric acid; and GLY, glyoxal

that the proper selection of the cross-linker in a chitosan system is necessary. Swelling characteristics of chitosan with different natures of cross-linkers each at 4% concentration have been shown in Fig. 7.

In a study, nanocapsules of aloe vera encapsulating tragacanth gum were prepared using sonochemical microemulsion technique which displayed cell viability of 98% against human fibroblast cells along with good antimicrobial activity [63]. Aloin containing chitosan/alginate and chitosan/xanthan membranes were also developed as potential wound care membranes. The membranes obtained revealed excellent mechanical and swelling properties. Release of aloin was controlled by cross-linking with calcium ions; however, 100% aloin was not released due to the formation of hydrogen bonds with polysaccharides, as aloin consists of six hydroxyl groups in its structure [64]. In another study, chitosan has been blended with gelatin to prepare a gel matrix followed by the incorporation of aloe vera and transformation into a freeze-dried scaffold to generate a porous structure [65].

Biodegradation of the matrix was investigated for a period of 28 days where 70–80% scaffold degraded suggesting a faster rate of the material disappearance from the site. Lyophilized membranes of chitosan/collagen/Aloe vera composite have been found to be biodegradable and biocompatible wherein the polysaccharides of Aloe vera possibly interact with chitosan and collagen through hydrogen bonding or ionic interactions to form a stable matrix. It has been postulated that Aloe vera disorganizes and stabilizes the collagen structure and makes it more hydrophilic, protecting it from enzymatic attack, thereby increasing the rate of degradation. Cell proliferation as well as excretion of ECM by the seeded mammalian cells was observed with Aloe vera-incorporated membranes attributed to its mannose-rich polysaccharides [66].

The combination of Aloe vera and chitosan has been extended from membranes and films to electrospun mats wherein the release of anthraquinone in Aloe vera from chitosan has been investigated by Ibrahim et al. Aloe vera was found to be encapsulated, and 50% of it was released within 4 min. This may have an application in rapid drug eluting mats for immediate action in wounds especially in the initial phase of healing [67].

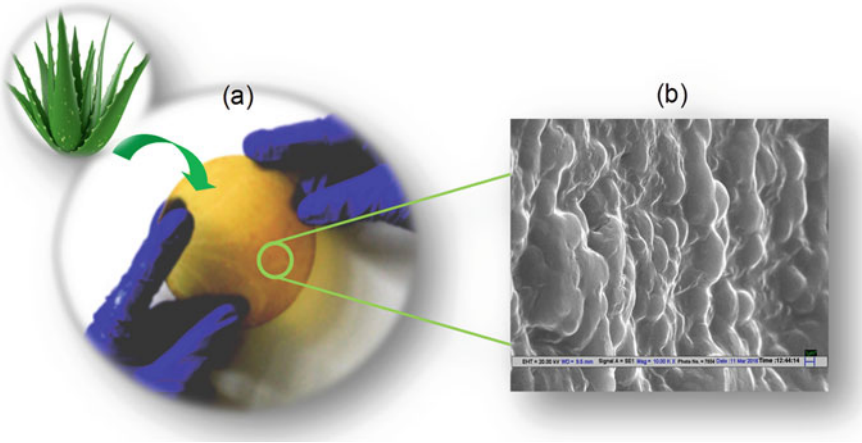

Fig. 8 (**a**) Pictomicrograph of chitosan/aloe vera nanobiocomposite wound dressing depicting uniformity and homogeneity and (**b**) SEM micrograph showing embedded aloe vera moieties within the chitosan nanobiocomposite membrane

Moving to nanocomposites, polysaccharide-based nanocomposites are an upcoming and interesting research area that allows the fabrication of nanoconstructs possessing architectural attributes and morphological resemblance to the natural ECM. Nanobiocomposite membranes where nanosoy was blended within the dextran and chitosan matrix were developed as shown in Fig. 8 [68, 69].

Further, aloe vera was used in the range of 10–40% to get membranes with a broad range of aloe content to fabricate chitosan/aloe vera nanobiocomposite dressings [69]. It was found that the 20% aloe vera content showed 99.4% antimicrobial activity against *S. aureus*. The wound healing pattern of these nanobiocomposite membranes was then observed using a BALB/**c** male Swiss albino mice model that indicated excellent scar prevention efficacy at the wound site post-21st day for dressings immobilized with aloe vera.

In addition, chitosan/aloe vera nanobiocomposite dressings strongly accelerated the rate of wound closure as compared to chitosan nanobiocomposite dressings due to the presence of acemannan, a major component in aloe vera that displayed immunomodulatory effect by upregulation of phagocytosis and anti-inflammatory characteristics [69]. Further, immunomodulatory effect fastens the process of wound healing and enhances the proliferation of fibroblasts, thus resulting in an increased ordered collagen deposition leading to effective scar prevention as seen in Fig. 9.

Histological examination was also conducted on excised healthy tissue post-21 days for reinforced chitosan/dextran nanobiocomposite and chitosan/aloe vera nanobiocomposite dressings as shown in Fig. 10.

Aloe vera-loaded nanocomposite displayed enhanced collagen organization and deposition along with a thin layer of epidermis. Pronounced hair follicles confirming diminished scar formation and inflammatory cell infiltration were visible along with

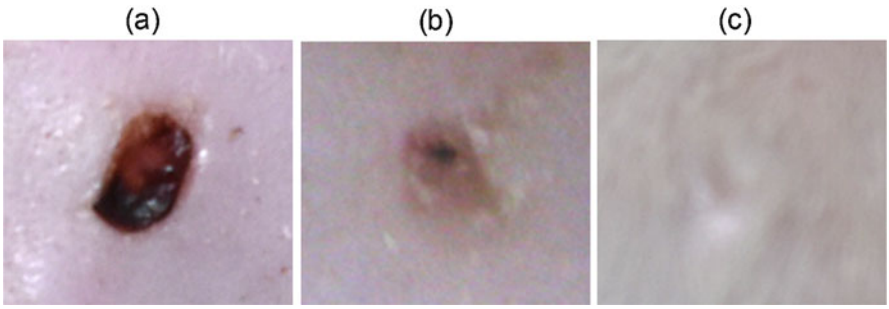

Fig. 9 Macroscopic appearance of wound repair on male Swiss albino mice of BALB/c strain post-days: (**a**) spontaneous healing, (**b**) chitosan nanobiocomposite dressing, and (**c**) chitosan/aloe vera nanobiocomposite dressing

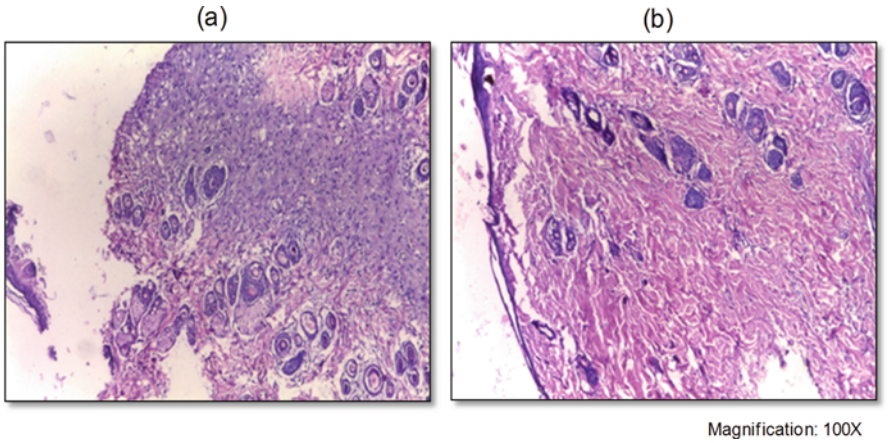

Fig. 10 Histological analysis of excised wound tissue on day 21: (**a**) chitosan nanobiocomposite dressing and (**b**) chitosan/aloe vera nanobiocomposite dressing

neovascularization (Fig. 10b) in comparison to the dressings without aloe vera that displayed lack of sufficient collagen deposition and infiltration of inflammatory cells leading to incomplete wound healing as revealed in Fig. 10a.

5 Conclusion

Wound care systems need to be designed in such a way that they offer a high level of biocompatibility and faster healing with minimum scar formation. The biomaterials discussed in the chapter are based on natural resources that render the material non-cytotoxic over widely used synthetic wound dressings containing silver nitrate, silver oxide, and nanosilver. Their fabrication process involves facile methodology and cheap herbal biomass. Such dressings have the potential to exhibit complete

aversion of microbial infection at the wound site resulting in reduced local tissue damage and systemic inflammatory responses that lead to high mortality rate. The economical approach discussed here can sufficiently enrich the assortment of topical medications available for the treatment of wounds for the great mass of the population, thus changing the social structure in terms of therapeutic outputs. A precise combination of natural polymers and bioactive component is needed so that the process of wound repair is accelerated. Aloe vera has made a big difference and leads the way to combine with polysaccharides, chitosan in particular, to develop dressings that not only control the infection at the wound site but also show proper healing of the wound.

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Synthesis and Applications of Carbohydrate-Based Hydrogels

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Abstract

Carbohydrate-based hydrogels are cross-linked three-dimensional structures of polymers, utilized for several purposes such as cell culturing, regenerative medicine, agriculture, contact lenses, biosensors, drug delivery, and tissue developing technology. The primary aim of this chapter is to review the literature regarding the classification of the carbohydrate-based hydrogels on the basis of their chemical structure, synthesis, and viability of their utilization. It also involved technologies adopted for hydrogel manufacturing. Hydrogels are most of the times manufactured from polar monomeric units. Based on the substrate material, they can be classified into natural polymer hydrogels, synthetic polymer hydrogels, and combinations of the two classes. Different fabrication processes such as polymerization, grafting, physical and chemical cross-linking, solution polymerization, and polymerization by irradiation are being discussed in this chapter. The synthesis of hydrogels is based on required applications. So this chapter also includes applications of carbohydrate-based hydrogels.

Keywords

Carbohydrates · Hydrogels · Pollution control · Bio materials · Polymerization · Cross-linking · Drug delivery

1 Introduction

Hydrogels are polymeric and hydrophilic and have 3D frameworks. They have the capability to absorb the great amounts of water and other liquids present in the living systems. Hydrogels can be chemically stable or they can get disintegrated and dissolve. They have high water contents, porosity, and a soft texture because of this reason; their ability to stimulate living tissues is greater than any other biological synthetic material [1]. If the network is formed by the molecular interactions or by the secondary forces such as ionic, H-bonding, or hydrophobic forces, then these membranes are called as “reversible” or “physical” gels. Most of the times, physical gels are reversible, and they get dissolved in the solvent, depending upon the physical conditions such as pH, temperature, or the ionic strength of the solution. Another type of such gels is called chemical or permanent gels. In these membranes, the framework is formed by the macromolecular chains bonded by the covalent bonds. This sort of cross-linking can be achieved in both dry and solution form [2]. The gels can also be categorized as charged or non-charged contingent to the functional group moieties present in the structure. Hydrogels which are categorized as charged usually show changes in swelling when the physical conditions like pH are altered. They also show variations in numbers when they are subjected to the electric field [3]. The hydrogels were first prepared by Wichterle and Lím (1960) [4]. They have multiple applications in the various areas such as in foodstuff, organic materials, farming, water treatment, etc. In the past few years, scientist have revealed that the hydrogels can be used in drug distribution [5], tissue developing

technology [6], sensors [7], contact lenses [8], etc. Several synthetic polymer hydrogels have been developed such as those formed by cross-linking poly(ethylene glycol) [9], poly(vinyl alcohol) [10], poly(amido-amine) [11], poly(*N*-isopropylacrylamide) [12], polyacrylamide [13], and poly(acrylic acid) [14] and their copolymers [15]. The synthetic hydrogels are more advantageous as compared to the natural hydrogels. For instance, the synthetic hydrogels have the ability of photopolymerization, adjustable mechanical properties, considerable control over the chemical composition, and scaffold architecture [16]. They have applications in the field of biomaterials because they are safe to use, hydrophilic in nature, biocompatible, and biodegradable. Hydrogels are synthesized from a huge diversity of materials and have vast-ranging applications. This chapter aims at highlighting the fabrication and application of carbohydrate-based hydrogels where carbohydrates are biological molecules. In a molecule of a carbohydrate, hydrogen and oxygen are present in the ratio similar to that of water. These molecules have empirical formula of $C_m(H_2O)_n$,where m and n can both be a similar or different number [17]. Some exceptions to the formula also exist such as in deoxyribose, a DNA carbohydrate [18] with the empirical formula of $C_5H_{10}O_4$ [19]. Carbohydrates can also be described as the hydrates of the carbon [20]; in terms of structure, they can also be regarded as the polyhydroxy ketones and aldehydes [21]. Various hydrogels have been synthesized by the natural carbohydrates such as hyaluronate [22], alginate [23], starch [24], cellulose [25], and chitosan [26]. The hydrogels based on these carbohydrates will be discussed in this chapter considering the fact that this selective information will be helpful to explore further ventures in the field of synthetic hydrogels.

2 Synthesis of Carbohydrates-Based Hydrogels

2.1 Synthesis of Cellulose-Based Hydrogels

Cellulose is a biopolymer. It is a polysaccharide comprising of linear chain of several thousands of β(1→4) linked D-glucose units. It is a significant structural component of the cell wall of algae, marine animals, plants, and oomycetes. It has low cytotoxicity. It is also secreted by some species of bacteria. It is the biopolymer which is found on the surface of the earth in greater quantity than any other polymer. Cellulose hydrogels have been prepared by the help of a solution of cellulose via the physical cross-linking as shown in Fig. 1. Cellulose contains several hydroxyl groups which can make the hydrogen-bonded network. The major issue in preparing cellulose-based hydrogels is the selection of the appropriate solvent as it does not dissolve in all the solvents [27]. Different types of solvent systems have been used for this purpose such as *N*-methylmorpholine-*N*-oxide (NMMO) [28] and alkali/urea (or thiourea) [29]. Several solutions are fabricated to solubilize the cellulose. This provides opportunities for the development of cellulose hydrogels.

Lithium chloride/dimethylacetamide (LiCl/DMAc) as a solvent has been used to dissolve native cellulose to fabricate the hydrogels [30]. A cellulose-based hydrogel

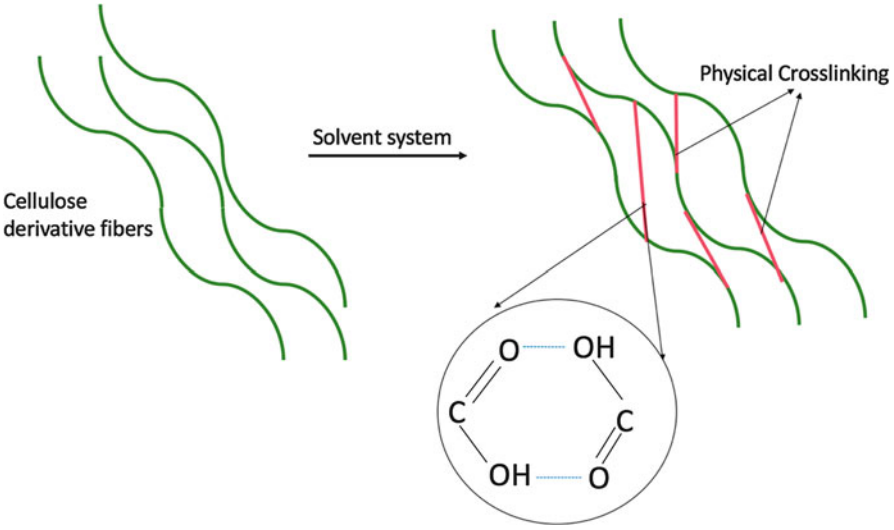

Fig. 1 Physical cross-linking of cellulose hydrogels

in the form of the beads has been prepared by Glasser et al., by drop addition of the cellulose, lithium chloride (LiCl), and dimethylacetamide (DMAc) solution into the non-solvent system such as azeotropic mixture of methanol or isopropanol [31].

The *N*-methylmorpholine-*N*-oxide (NMMO) provides us with a physical technology for the production of cellulose fibers, films, food cases, membranes, sponges, beads, and others without any harmful by-products [28]. A solution of high molecular mass cellulose can be prepared by dissolving it in NMMO/H_2O at elevated temperatures to make the clear solution. The crystal lattice of cellulose changes to an amorphous form when the molecules of NMMO start moving at 100 °C. At this point, the cellulose molecules start replacing the water molecules which are attached to NMMO, when the whole mixture is heated at 150 °C [32].

Cellulose solubilized in hydrophilic liquids consisting of ions, for instance, -butyl-3-methylimidazolium chloride (BMIMCl) and 1-allyl-3-methylimidazolium chloride (AMIMCl) [33]. The regenerated products have been gained by adding water, acetone, and ethanol. By making the alteration in the regeneration process and instrument, the regenerated cellulose material can be transformed into various forms such as beads, films, and gels [34]. The cellulose hydrogels can be made by redeveloping the cellulose solution from its ionic liquid (1-allyl-3-methylimidazolium chloride, AMIMCl) [35], and deionized water was used as the coagulant. Flexible cellulose hydrogels are prepared by making the solution of cellulose in 1-butyl-3-methylimidazolium chloride and then leaving the solution at 25° C for 7 days [36].

A novel solvent for dissolving cellulose has also been prepared. In this solvent, 7% by weight NaOH was mixed with 12% by weight of urea in water which is precooled at −12° C. In this solution, the 105 order weight of cellulose can dissolve

rapidly. The dissolution of cellulose occurs at low temperature among the small molecule of the solvent such as in the solution of urea, NaOH, and water and macromolecules of cellulose [37].

Another method for the preparation of cellulose-based hydrogel membranes is reported by the use of NaOH (9.5% by weight) and thiourea (4.5% by weight) aqueous solutions which are cooled at −5° C as solvent [38]. These hydrogels have also been prepared by cross-linking them physically with the macromolecule chains within the solutions at high temperatures. Cellulose hydrogel membranes can be created by pre-gelation method in the solvent system of NaOH/thiourea [29].

The stability of the structure and the efficient swelling of the cellulose hydrogels mostly depend on the chemically linked cross-networks. Di-functional molecules are employed as the cross-linkers for cellulose and cellulose derivative-based hydrogels in order to bind the different polymer molecules with the covalent bond in a 3D hydrophilic network. It has been investigated that cross-linking of the carboxymethylcellulose (CMC) and hydroxyethylcellulose (HEC) with the divinylsulfone makes the cellulose-based hydrogels superabsorbents [39]. Such poly ionic hydrogels display extreme sensitivity and the sorption ability to ionic strength variations and the pH of the external solutions [40].

2.2 Synthesis of Hyaluronic Acid-Based Hydrogels

Hyaluronic acid is very vital for cartilage repair [41]. It is one of the main constituents of cartilage where it imparts the functional and structural integrity to the tissue. It is completely biocompatible and bio-resorbable; along with this it also plays a significant vital role in the synthesis of hyaline tissue. Hyaluronic acid-based hydrogels are prepared by several methods [42]. Physically and chemically cross-linked hyaluronate (HA) hydrogel membrane which is used for the cartilage repair can be synthesized by the chemically cross-linked HA derivatives as shown in Fig. 2.

The unmodified and the derivatives of HA were dissolved in the 0.15 M solution of NaCl and then the whole solution was incubated at 37 °C. The rheological behavior of the sample was studied at 1, 7, 14, and 21 days. The solutions were later dialyzed against water at 48 h. Then, it was freeze-dried. After extensive washing of the product with the ethanol, the substitution ratios on C^{12} of the polymer was determined by gas chromatography, and the average molar masses of HA were determined by the SEC-MALLS [43].

Photopolymerized hyaluronic acid-based hydrogels can be synthesized with the solid methacrylated HA (HA-Ac) or the common HA. HA-Ac or HA was dissolved in a 4-(2-hydroxyethyl)-1-piprazeneethanesulfonic acid (HEPES) saline buffer containing triethanolamine, *N*-vinyl pyrrolidone (NVP), and eosin Y in fixed ratios and concentrations. Further, the solutions were illuminated with the xenon lamp for 1 min at 480–520 nm and 75 W/cm^2. For the mechanical modulation of the HA-based hydrogels, variable quantities of poly(ethylene glycol)–propion-dialdehyde(PEG-DA) or peptide-modified PEG-DA were added prior to the photopolymerization [44].

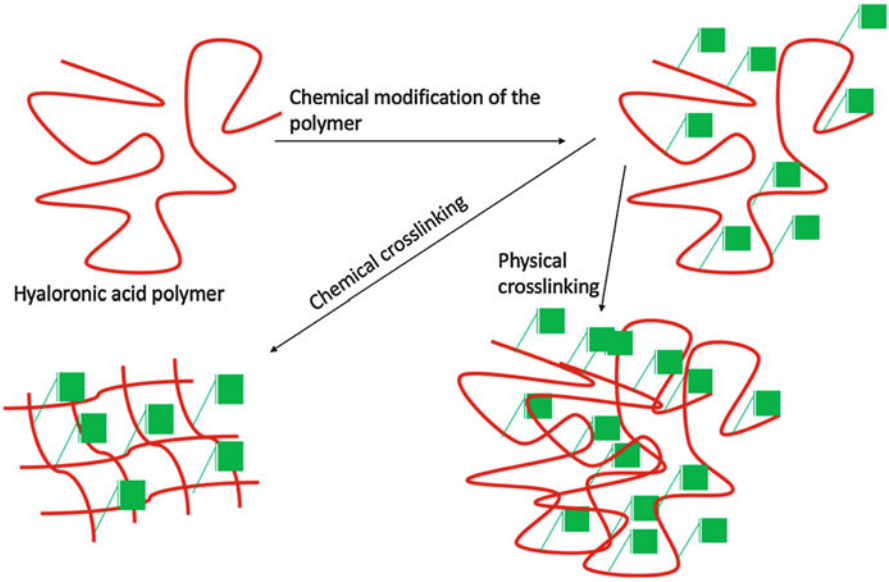

Fig. 2 Physical and chemical cross-linking of hyaloronic acid-based hydrogels

The HA-based hydrogel films can also be synthesized with the hyaluronic acid–adipic dihydrazide (HA–ADH) product. This product is prepared by dissolving the HA in water and then adding the ADH with continuous stirring. Afterward, the pH of the solution is adjusted by the HCl and later on adding the 1-ethyl-3-[3-(dimethylamino)-propyl]carbodiimide (EDCL). In order to prepare the HA-PEG hydrogel membrane, 5 mg/ml of hyaluronic acid–adipic dihydrazide(HA–ADH) is dissolved in H_2O. Poly (ethylene glycol)–propiondialdehyde (PEG-diald) is then dissolved in water at the concentration of 50 mg/ml separately. Fixed volumes of both solutions are then added to the petri dish. In order to obtain the equimolar equivalents of the hydrazide and aldehyde moieties, the mixture is gently swirled. The hydrogel begins to firm within 60 s of mixing the solutions. In order to obtain the uniform solid hydrogel, the mixture is agitated on the orbital platform for about 24 h. Hydrogels are then kept in open dishes for the whole night at 37° C to evaporate the solvent. After this, hydratable, flexible HA hydrogel films can be obtained [45].

For the injectable cell delivery, ionically cross-linked hyaluronate-based hydrogels are used. These hydrogels can be prepared by the hyaluronate-g-alginate. For this purpose alginate samples were modified with the arginylglycylaspartic acid (RGD) peptides to enhance the cellular interactions. Later on, a peptide with the sequence of (glycine)4-arginine-glycine-aspartic acid-serine-proline was added to the alginate solution along with the 1-ethyl-3-(dimethylaminopropyl) carbodiimide and *N*-hydroxysulfosuccinimide with vigorous stirring. The reaction was continued for 20 h at room temperature. Afterward, the solution was purified by dialyzing

against water for 4 days and then was treated with charcoal. After this, the solution was filtered for sterilization and lyphlized at −20 °C. Then, NH_2-hyaluronate was prepared with the similar method using ethylenediamine, EDC, and NHS. Then it was conjugated with the alginate. Afterward, alginate was coupled with the NH_2-hyaluronate by carbodiimide chemistry [46].

Thiolated hyaluronan-based hydrogels can be prepared with the glutathione. They are used for ophthalmic applications. For the fabrication of thiol-modified gelatin or denatured collagen (gelin-S) containing hydrogels, thiol-modified carboxymethyl hyaluronic acid (CMHA-S) and gelin-S were dissolved by the sterile in degassed water to obtain 1% w/v solutions. Glutathione disulfide (GSSG) was re-suspended in the solution of 1 phosphate-buffered saline (PBS) with the pH 7.2. The CMHA-S and gelin-S solutions were mixed in a ratio of 1:1 by volume. 1 volume of GSSG solution was then added to 4 volumes of the thiolated hyaluronic acid solution. After both the solutions were mixed with each other, the gel started to form within 5 min [47].

Injectable hyaluronic acid hydrogels by dual cross-linking can be prepared in order to be used as a potential cell or drug carrier. Such membranes can be synthesized with vinyl sulfonate triblock copolymer. Thiolated hyaluronic acid (HA-SH) was prepared by derivatizing the HA with thiol groups. Then both of the polymers were dissolved in phosphate buffer solution separately. After both the polymers were completely dissolved, then HA-SH was added to the triblock copolymer solution. The mixture was immediately placed in a pre-heated oven at 37 °C. This was done to allow thermal gelation and the accompanying Michael addition cross-linking of the thiol and vinyl sulfone groups as shown in Fig. 3 [48].

For the prevention of post-operative adhesion (after the surgical procedure is performed on the body), chitosan and hyaluronic acid-based hydrogels can be used. Chitosan was modified in the presence of isopropyl alcohol, sodium hydroxide, and monochloro-acetic acid. The dry product was taken after vacuum drying. The product was named as *N*, *O*-carboxymethyl chitosan (NOCC). The aldehyde hyaluronic acid (A-HA) was made from HA with the addition of ethylene glycol and pre-iodate. The NOCC/A-HA hydrogels were created by the cross-linking of NOCC and A-HA. Both of these compounds were dissolved in normal saline solution at different concentrations. Then the hydrogels were obtained after mixing both the solution in a ratio of 1:1 [49].

In order to study megakaryocytes, hyaluronan-based hydrogels are used. Such hydrogels can be fabricated by using free radical cross-linking. For its synthesis, these radicals were initiated by light. The metacrylated hyaluronan (MeHa) was dissolved in phosphate saline which contained 0.05% 2-methyl-1-[4-(hydroxyethoxy)phenyl]-2-methyl-1-propanone. Afterward, they were polymerized with the help of 4 mW/cm^2 ultraviolet light from a long-wave ultraviolet lamp and suspended into the 50 μl of 2% MeHa 0.05% Irgacure 2959 solution. Later on, to serve the purpose of cross-linking, human type IV collagen or human plasma fibronectin was placed into sterile syringe tip mold and exposed to UV radiations [50].

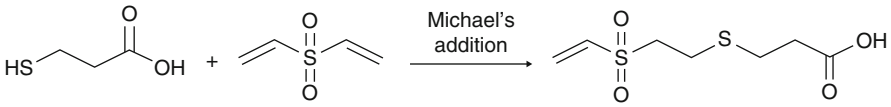

Fig. 3 Schematic representation of Michael's addition

2.3 Synthesis of Chitosan-Based Hydrogels

Chitosan is produced by restricted de-acetylation of chitin. It is an organic biopolymer and a linear polysaccharide. It is a major component of crustacean shells. It has excellent biological properties such as nontoxicity, biodegradability, inertness, and affinity toward proteins [51]. Chitosan-based hydrogels can also be prepared by several methods. Water-soluble photopolymerizeable chitosan hydrogels are used for bio-fabrication. Such hydrogels are fabricated by chitosan which was isolated from deacylated chitin and converted into the water-soluble form as shown in Fig. 4. Chitosan-based photo-polymerizable hydrogels can be prepared by the following method represented in Fig. 4. Further, the chemical modification is done by the addition of glycidyl methacrylate moieties to the chitosan (CH) framework in a phosphate-buffered saline (PBS)/dimethylformamide (DMF) solution, so as to create the CH-glycidyl methacrylate (CHGM) conjugates [52].

Chitosan hydrogels have also been used in tissue engineering. For making a type of these hydrogels, chitosan and graphene are employed. Such hydrogels are synthesized by adding chitosan powder to the aqueous graphene dispersion. Afterward lactic acid is added to the mixture with continuous stirring. Then the sample is sonicated to achieve a homogenous dispersion. Later on, the solution is cast on the petri dish and left to be dried at 50 °C. The excess of the lactic acid is removed by washing with the ethanol/phosphate-buffered saline (PBS). Afterward, dried films were obtained by vacuum drying at 50 °C [53].

For the controlled drug delivery, cyclodextrin-grafted chitosan hydrogels are used. For fabrication of these hydrogels, carboxymethyl chitosan (CMC) and carboxymethyl cyclodextrin (CMCD) are being utilized. Both of these are synthesized from cyclodextrin (CD). For the preparation of such membranes, CMC, anhydrous glucose unit (AGU), and CMCD are dissolved in distilled water in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) and *N*-hydroxysuccinimide (NHS). The reaction is carried out at room temperature for 24 h with continuous stirring at 300 rpm. The resultant solution obtained is highly viscous. It is precipitated in methanol and then filtered. The product obtained is allowed to swell with distilled water. The resulting hydrogel is then dialyzed against deionized water. The hydrogel thus obtained is under pressure at 40 °C [54].

Chitosan hydrogels are used for tissue engineering. Such hydrogels are photopolymerizable and can be prepared by glycol chitosan. Glycol chitosan is modified to methacrylated glycol chitosan (MeGC) by the addition of glycidyl methacrylate into the amine groups of chitosan. Later on, the stock solution of MeGC is prepared

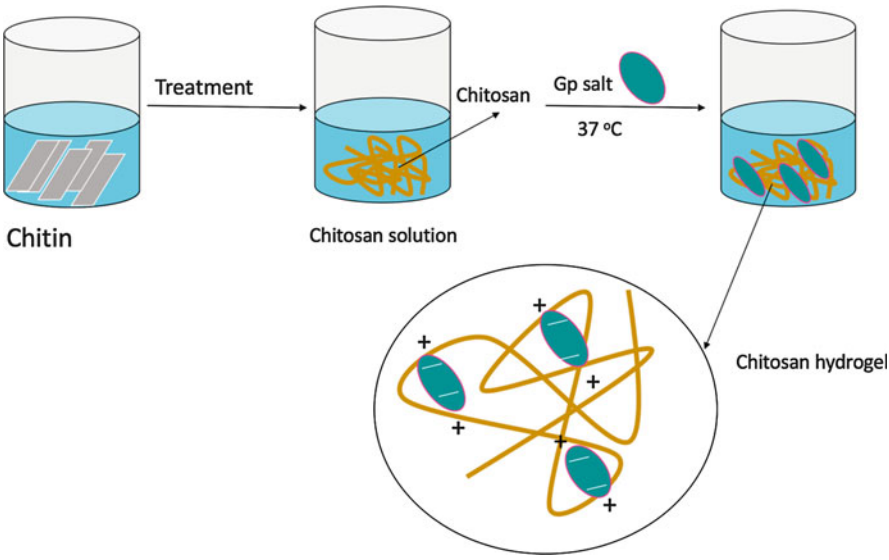

Fig. 4 Schematic representation of the fabrication of chitosan-based hydrogels

in phosphate saline buffer. The solution is exposed to blue light in the presence camphorquinone (CQ), fluorescein (FR), and riboflavin (RF) as the photoinitiator [55].

Chitosan hydrogels are used for cellular adhesion. For the fabrication of these hydrogels, chitosan is dissolved in 1% solution of acetic acid, and a separate solution of genipin (Gp) is prepared in ethanol. The hydrogels can then be fabricated by blending both solutions with vigorous stirring at room temperature for 10 min. The mixed solutions are then poured into the petri dish and placed in the incubator for 48 h at 37° C. Later on, glycine solution is added to the gels and incubated for 2 h to bind the unreacted Gp in the gels. Afterward, the glycine solution is removed from the gels and washing is done [56].

The composite chitosan hydrogels are excellent for the release of the hydrophobic drugs. In order to fabricate these membranes, chitosan is dissolved in acetic acid and then the pH of the solution is increased by the addition of NaOH with continuous stirring. Now, this whole mixture is used for the preparation of polymeric gels. The solution is prepared for the composite gels in a similar manner with the addition of some micro emulsion (ME). Then genipin is added to both chitosan solutions and they are thoroughly mixed together. Later on, the mixture is transferred to the circular mold made up of polyvinyl chloride (PVC) and left there to cure at room temperature for 20 h. In the end the composite chitosan hydrogel is obtained [57].

Biocompatible chitosan hydrogels are used for making nanofibrous biomaterials with high strength. In a recent study, chitosan obtained from the shells of shrimps is employed for this purpose. The chitosan is dissolved in alkaline aqueous solution containing LiOH/KOH/urea/H_2O in the fixed ratios. The solution is prepared and

refrigerated at −30 °C until it is completely frozen. Afterward, the frozen material is completely defrosted and stirred vigorously at room temperature. The trapped air and bubbles are removed by centrifugation at 7000 rpm, at 5 °C for about 10 min. The resultant is transparent chitosan solution. This solution is casted on the glass plate in the thickness of about 1 mm. Then the glass plate is immersed in the hot water coagulation bath for 30 min to obtain a physical chitosan hydrogel. This gel is thoroughly washed by the distilled water [58].

2.4 Synthesis of Alginate-Based Hydrogels

Alginate is a biopolymer. It is an organic linear polysaccharide which is extracted from brown algae. It consists of the alternating blocks of 1–4 linked alpha L-guluronic and beta D-mannuronic acid deposits. It is the most highly employed polymer matrix because of its nontoxicity, excellent biocompatibility, and easy gel-making ability [59].

The most commonly employed method for the gelation of alginate is through the exchange of the of sodium ions of glucuronic acid with the divalent ions. The alginate hydrogels show different affinities with cations; hence, with each new ion, a hydrogel is formed with different permeability, strength, and stability [60].

Dripping method is also used for the fabrication of alginate hydrogels. Dispersion of alginate sol is required for bead production. Alginate liquid droplets are thrust out by a nozzle into the gaseous phase and are dropped into the gelling bath which contains divalent cations such as Ca^{2+}, Sr^{2+}, etc., to make the cross-linked alginate beads as shown in Fig. 5. The efficiency of alginate beads creation can be enhanced by making a laminar liquid jet with increasing the volumetric flow rate of the alginate sol. If this liquid jet is allowed to break up naturally, then alginate beads are formed. With the help of this method, alginate droplets of 2 mm diameter can be produced. The size of the detached droplets in jetting regimes is primarily influenced by the inner diameter of the nozzle and the viscosity of the alginate sol [61].

Alginate-based hydrogels can also be prepared by the atomization process. In this method, the alginate sol is dispersed into the sol which is then to form the micro-particles. The sol can be atomized by using different methods such as by rotary atomization, co-axial nozzle, or pressure nozzle. In the rotary atomization, the alginate sol is put on to a disk-like apparatus that operates at high speeds. This results in the production of centrifugal force which spreads the sol into a thin film on the surface of the disk as shown in Fig. 6. This method is easy to use and is commonly employed in the industry. In the co-axial atomization, the apparatus drags the sol which eventually disintegrates into the fine particles. In this process, the sol is extruded at high velocities along with the flowing stream of air. In pressure atomization, the sol is extruded from the nozzle at very high velocity into the still air and is then integrated into the droplets via the drag force operating between the fluids [62].

Non-channeled emulsification is also used for the production of alginate hydrogels. In this, mechanical stirring is used around 100 rpm for the production

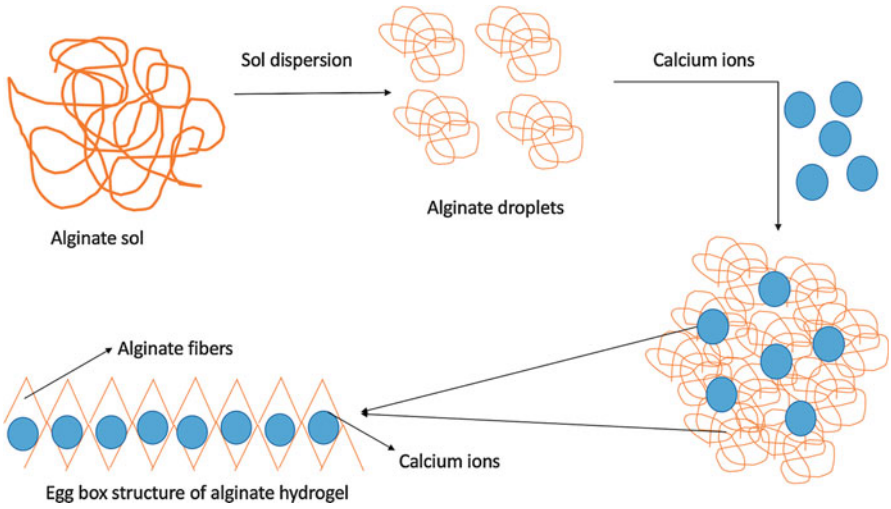

Fig. 5 Schematic representation of fabrication of alginate-based hydrogels

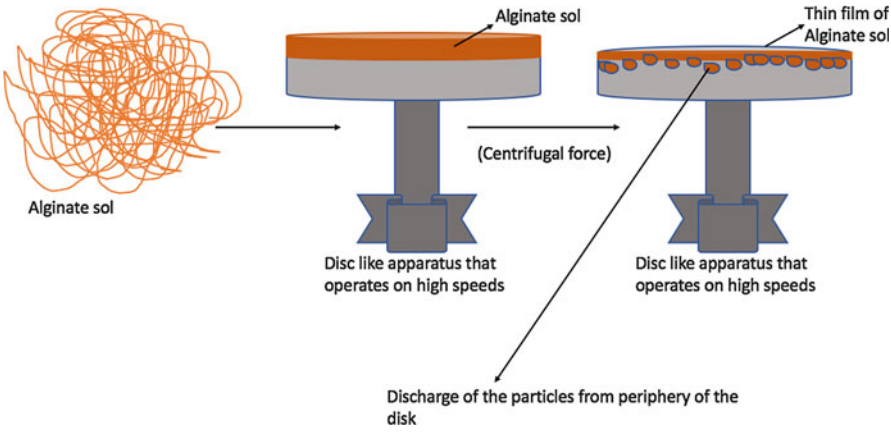

Fig. 6 Rotary atomization of alginate sol

of atomized particles. However, the size of the particle is inversely proportional to the energy of agitation. By the help of this method, a large range of particles of mean size between 20 and 1000 m are formed. The distribution of particle size is generally broad and poly-dispersed [63]. The droplets formed by the dispersion of the sol are then gelled. This is done by cross-linking the alginate polymeric chains with the divalent cations such as that of calcium and strontium. Divalent cations are used as they can bind to the guluronate blocks of the polymer chains forming an enclosed egg cage or shell-type structure [64].

External gelation is a most widely used method for the production of alginate hydrogels. In this method, calcium ions are introduced externally into the already

Table 1 Comparison of alginate gelation techniques

Technique	Production	Applications	Reference
External gelation	Asymmetrical beads		[61, 62]
Internal gelation	Symmetrical beads	Biotechnology and food	[62, 64]
Ionotropic/interfacial gelation	Oil core microcapsules	Controlled-release of various liquids	[64]
Atomization	Microparticles	Drug release	[57]
Inverse gelation	Microencapsulation of linalool	Insecticide	[63]

dispersed alginate droplets. The ions diffuse into interstitial places present between the polymeric chains of the alginate. When both made contact, the ions begin to cross-link with the polymer chains at the alginate droplet's periphery. This causes the initial formation of a semi-solid mass which encases the droplet with a liquid mass [65]. The sol which is now engulfing the liquid is ultimately converted into the gel capsules formed by the external gelation [66].

Another process for the gelation of alginate polymer is internal gelation. In external gelation, the coagulation of calcium ions occurs which renders the system ineffective. In the internal gelation technique, the alginate emulsion which also contains a dispersion of calcium carbonate particles is emulsified into the oil phase. Later on, acetic acid is added to the emulsion to lower the pH as well as to create the dispersion of the calcium ions with the subsequent release of carbon dioxide and water. The released calcium ions then cross-linked with the alginate polymer. As the cross-linking occurs inside the alginate droplet, the gelation is known as internal gelation. In this type of gelation, an immiscible liquid is used for the dispersion the alginate sol [67].

The alginate hydrogels can also be fabricated by the process of inverse gelation. In this process, an aqueous solution or oil containing calcium ions is thrust out through a nozzle into the bath of alginate solution. On contact, calcium ions are moved to the periphery and get cross-linked ionotropically with polymeric chains of alginate. At the end of this process, the initial liquid drops are encased by the continuous Ca-alginate semipermeable membrane. This method is only used when the liquid core droplets are generated by the liquid air methods [68]. Other gelation processes are also used to make alginate hydrogels such as interfacial gelation, which is comparatively new and occurs at the face of immiscible liquids [69]. A brief comparison of various gelation techniques and their end product is represented in Table 1.

2.5 Synthesis of Hemicellulose-Based Hydrogels

Hemicellulose is a matrix polysaccharide and is also known as the polyose. It is present alongside the cellulose in most of the plant cells [70]. Hemicellulose is extracted alongside the cellulose by fractional separation. It has an amorphous structure and has little strength, whereas cellulose is crystalline in structure.

Cellulose is strong in comparison to hemicellulose and is completely resistant to hydrolysis. It can hydrolyze easily by the myriad hemicellulose enzyme or by the dilute acid or base. It is a hetropolymer and has different types of sugar monomers. It consists of shorter chains in comparison to the cellulose; also the chains of hemicellulose are branched. In addition to glucose, it also contains arabinose, mannose, rhamnose, galactose, and xylose [71].

Hemicellulose-based hydrogels are prepared by several methods. 2-[(1-Imidazolyl)formyloxy]ethyl methacrylate (HEMA-Im) can be prepared by dissolving 1,19-carbonyldiimidazole and 2-hydroxyethyl methacrylate (HEMA) in chloroform at room temperature. Hemicellulose is modified by making the solution of hemicellulose in anhydrous dimethyl sulfoxide (DMSO); HEMA-Im is also added at later stages in the reaction. Triethylamine is used as the catalyst of the reaction. The product thus obtained is precipitated two times with the ethyl acetate [72]. Later on this product is polymerized in order to obtain the hydrogel. For that purpose the above hemicellulose and HEMA were dissolved in water in the presence of ammonium peroxodisulfate and sodium pyrosulfite. This solution is transferred to the circular sculpt of 1 mm thickness and heated to 40 °C for 30 min [73].

Hemicellulose hydrogel can also be prepared by the *N*-isopropylacrylamide. For this purpose, a derivative of hemicellulose is prepared with the maleic anhydride in the presence of dimethylformamide (DMF) and LiCl. The product obtained is named as Hce-MA. For the fabrication of hydrogel, the solution of Hce-MA and *N*-isopropylacrylamide is made in de-ionized water. The 2,2-dimethoxy-2-phenyl acetophenone (DMPA) dissolved in *N*-methyl-2-pyrrolidone (NMP) is added as the photo-initiator in the precursor solution. This precursor solution is then irradiated with UV lamp at 365 nm, 100 for about 10 h. The hydrogels thus obtained are then immersed in de-ionized water for 48 h at room temperature, in order to remove the unreacted substances [74].

Hemicellulose hydrogels can be fabricated by grafting them from wheat straw with a redox initiation system, in a water bath at 50 °C as shown in Fig. 7. For this purpose, hemicellulose (HC) is first dissolved in water at fixed concentration of 5% weight by weight. Potassium persulfate and anhydrous sodium sulfite are then added in this solution. Afterward, acrylic acid is added, before addition of soluble cross-linker *N*,-*N*-methylene bisacrylamide in this solution. The solution gets thicker. This mixture is then cut into cuboids and later on vacuum dried. The hydrogel thus obtained is then submerged in de-ionized water for 48 h; the water is changed at periodic intervals to remove the impurities, particularly the acrylic acid. The hydrogels obtained are then dried again in vacuum above 50 °C [75].

Xylan is a group of hemicellulose. A particular type of hydrogel can be prepared by xylan. For this purpose, the solutions of xylan and chitosan are prepared by mixing them in dry form and then stirred with acidified water. Afterward the solution is heated at 95 °C for 20 min. Hydrochloric acid is then added to the mixture. Then the solution is cooled at 25 °C and is poured into the polystyrene dishes. The solution is further dried to obtain the films of uniform thickness. The films are swelled into gels when placed into the water [76].

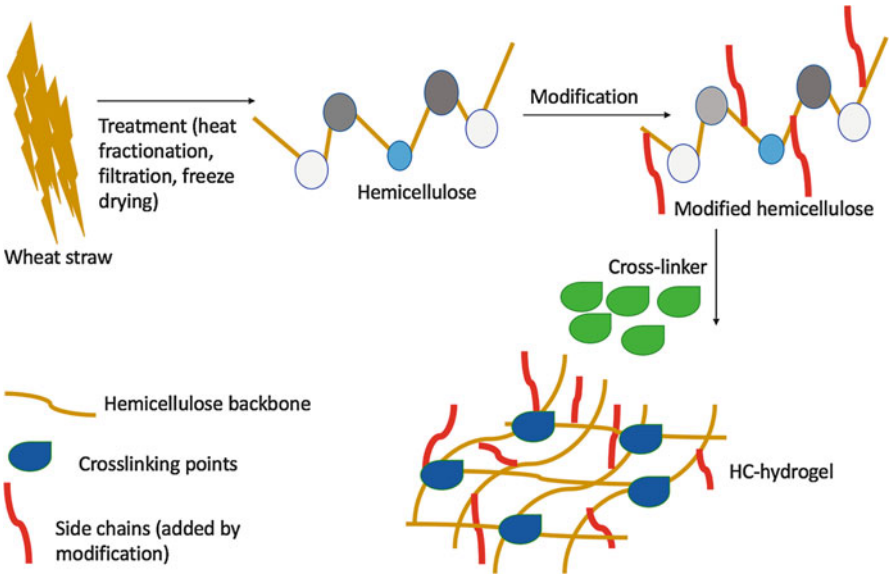

Fig. 7 Fabrication of hemicellulose-based hydrogel

Cationic HC hydrogel is prepared by the *O*-acetyl galactoglucomannan (GGM) which is hemicellulose. Firstly a derivative GGM-MA is prepared, which is made by inserting methacrylate (MA) into GGM. The GGM-MA is polymerized in the presence of 2-(methacryloyloxy) ethyl trimethylammonium chloride (MeDMA) and ammonium persulfate. The mixture thus formed is placed in a tube which is then put in the oil bath for 2 h at 75 °C. The formed hydrogel is placed in the deionized water so as to remove the unreacted substances. Afterward, the product is dried in the oven at 40 °C, and a GGM hydrogel is obtained [77].

Macroporous HC-based hydrogels are prepared from xylan type HC. The solution of isolated xylan in deionized water is stirred along with the 85 °C temperature for about 60 min, and then the solution is cooled at room temperature. This solution is continuously purged with N_2 gas for 10 min; afterward, ammonium persulfate and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TEMDA) are added, with stirring for 10 min. *N*,*N*-Methylenebisacrylamide (MBA) and acrylic acid are added successively with stirring for 2 h in the nitrogen atmosphere. Then, the reaction mixture is left without stirring for 24 h. The hydrogel thus obtained is washed with deionized water for 7 days. This product is further treated by 0.1 M NaOH solution in order to get the complete conversion of COOH groups to COO− groups (in the hydrogel). The hydrogel is then washed again with deionized water [78].

High strength hemicellulose can be made by freeze–thaw method. For this purpose, a solution of polyvinyl alcohol (PVA) is made in distilled water at 90 °C along with continuous stirring for about 30 min. Later on, the suspension of hemicelluloses and chitin nanowhiskers is made separately in water. The solutions are mixed in the fixed proportion of 1:1:1 along with the vigorous stirring at room

temperature; later on the temperature is slowly increased to 80 °C for 1 h. Then the mixture is cooled again to room temperature and is poured into a Teflon sculpt. Now the mixture is frozen for 10 h at −20 °C and successively thawed for 1 h at room temperature [79].

Temperature- and pH-sensitive hydrogels can also be prepared. In order to make these gels, solution of hemicelluloses and Na_2SO_4 is made in distilled water at 80 °C for 2 h with continuous stirring. Afterward, the solution is cooled at room temperature. The mixture is continuously being purged with N_2 for about 15 min. This mixture is subjected to glow discharge for about 90 s with varying applied voltages ranging from 500 to 650 V. After this, *N*-isopropyl acrylamide (NIPAAm) is added to the mixture, which is followed by the addition of *N*,*N*-methylene-bisacrylamide (MBA). Before the addition of MBA, monomers are completely dissolved. The mixture is then stirred for 2 h in the atmosphere of nitrogen gas. Afterward, the reaction mixture is left at room temperature for 24 h without stirring. At the end, dual-sensitive (pH and temperature) hydrogels are obtained [80].

3 Applications of Polysaccharides-Based Hydrogels

3.1 Applications of Cellulose-Based Hydrogels

Cellulose hydrogels are used for drug release as well as in restricted release. Assimilation of a secondary constituent into the hydrogel at varying concentrations can alter the network in terms of structure and morphology; in this way, the diffusion properties of the hydrogel membranes can also be controlled. Carboxymethyl cellulose (CMC) used in the hydrogels has increased the pore sizes because of the repulsion caused by the electronic cloud of carboxyl groups. This leads to a greater swelling ratio of the order of 1000 g^{-1}, along with the faster release of the protein drugs [25].

A negative thermo-sensitive hydrogel drug release system can be achieved by grafting *N*-isopropyl-acrylamide (NIPAAm) or *N*-vinylcaprolactam (NVCL) on cellulose or chitosan. The NVCL hydrogels displayed an inverse relationship of swelling with temperature and hence are used as on/off release systems, such as "swelling is on" which occurs at lower temperatures and "shrinking is on" which occurs at high temperature [81].

There are some cellulose hydrogels which can be inoculated to the body in the liquid form. Afterward, they develop into the gel inside the body. Inside the body, the temperature is higher than the lower critical solution temperature (LCST) of these gels. Thermoset hydrogel systems, such as chitosan/CMC, are the examples of such hydrogels. These hydrogels are made by neutral solutions of different thermal-responsive monomers of cellulose and chitosan. These hydrogels being thermally sensitive are extremely useful as biomaterials. These thermoset hydrogel systems are also employed as the directed drug transporters, hence eliminating the requirement of intrusive surgeries. These hydrogels most of the times sufficiently lengthen the release time because of the effective encasing of drugs inside them [82].

Cellulose hydrogels also have applications in tissue developing. It is a latest technology in which cellulose hydrogels are being used as frameworks to perform different functions of extracellular matrixes and to create novel tissues [83]. Cellulose has no antimicrobial action, which is required to block the infections. However, Ag or ZnO nanoparticles can be incorporated into the gel system to attain antimicrobial property [84]. Cellulose hydrogels have also been used for the purpose of water purification. The solubilized pollutant particles such as ions and molecules can enter easily inside the chitin or cellulose hydrogels and get attached to the certain functional groups such as amines ($–NH_2$) and hydroxyls (–OH) at particular values of pH [85].

One of the major uses of cellulose hydrogels is that they act as the auxiliary material for working additives, such as membranes which contain electrolytes that are employed in batteries or capacitors [86]. They also serve as the supporting material for porous aerogels which contains inorganic catalysts such as Ag [87] and TiO_2 [88] for heterogeneous catalysis.

3.2 Applications of Hyaluronic Acid-Based Hydrogels

Hyaluronic acid hydrogels also have a wide range of properties. The hyaluronate (HA)-based hydrogels which are produced by physical and chemical cross-linking are used for the cartilage repairing [43].

The HA hydrogels are used extensively because of their biocompatibility and very low protein absorption, which make them an excellent material against adhesions. It also acts as a type of enzymatically degradable and natural analogue of poly (ethylene glycol) diacrylate (PEG) [44]. Hyaluronic acid–adipic dihydrazide (HA–ADH) with poly(ethylene glycol)–propiondialdehyde (PEG–diald) cross-linked hydrogels served as a biomaterial for delivery of drugs [45].

Ionically cross-linked hyaluronate-based hydrogels are used for injectable delivery of drugs [46]. The thiolated hyaluronan-based hydrogels are used for ophthalmic applications. They are used in the treatment of the chronic corneal defects. They have shown a great deal of biocompatibility with eyes and skin [47]. HA is a non-sulfate, naturally found glycosaminoglycan and is widely used in tissue engineering and wound healing. HA has been recognized as the proliferation increasing agent of peritoneal mesothelial cells [89].

In the past years, many HA hydrogels have been used against adhesion because of their excellent gel-making properties. But HA-based hydrogels have very poor mechanical strengths along with the rapid degradation due to enzymatic actions. This limits the effectiveness in the prevention against adhesion. However, chemical modification of HA creates new biomaterials against adhesion. *N*, *O*-carboxymethyl chitosan (NOCC) and aldehyde hyaluronic acid (A-HA) are used to make the hydrogels; these hydrogels limit the disadvantages and enhance the effectiveness of chitosan hydrogels [54].

With the addition of fibronectin and type IV collagen in HA hydrogels, the proplatelet formation is increased. HA also serves as a superlative model for the production of hydrogel frameworks in order to directly visualize and study megakaryocytes (which are immersed in a mesh of extracellular matrix (Mk–ECM))

component interaction in 3D physiological environment. The biochemical and biomechanical properties of HA hydrogels enable it to copy the function of bone marrow; afterward, the Mk–ECM interactions and responses can be easily studied in this artificial environment, minimizing the external matrix factors which are present in the real environment (i.e., of bone marrow) [90].

3.3 Applications of Chitosan-Based Hydrogels

Chitosan has shown hemostatic properties [91]; these hemostatic effects can help in the prevention of postsurgical bleeding within the abdominal cavity. In addition to that, chitosan also shows antimicrobial activities [92].

The modified photocurable/photopolymerizeable water-soluble chitosan can allow the fabrication of two-photon polymerizible (2PP) biodegradable scaffolds for tissue engineering. A variety of required scaffold shapes can be fabricated and tested against different cell types regarding the particular cell–scaffold geometry interaction. In the areas of 3D scaffolding, 2PP can serve as a powerful tool which can overcome the limitations in fabrication of soft hydrogel materials on a subcellular level [52].

The cyclodextrin-grafted carboxymethyl chitosan hydrogels (CD-g-CMCs) depict excellent drug absorption/adsorption properties. When the acetylsalicylic acid or aspirin (ASA) are absorbed on CD-g-CMC hydrogels, they show slow and viable ASA release. The ASA release can be attributed to the formation of a host and guest complex between ASA and the hydrophobic cavity of CD in the hydrogels. This property of CD-g-CMC hydrogels can allow them to be applied as carriers of controlled drug delivery systems [54].

Type-II collagen (Col II) hydrogels are enhanced by chitosan. Such hydrogels have a high capacity for acting as an injectable scaffolding system which is used in cartilage repair. The scheme of incorporating the appropriate natural extra cellular matrix components within a cross-linked chitosan network is a valuable way of making a micro-environment which is capable of promoting tissue regeneration [93].

The chitosan hydrogels produced by the furfural derivative shows remarkable viscoelastic properties, which shows an interesting controlled release of drugs or other materials [55]. The composite chitosan hydrogels which are encapsulated by polyvinylchloride (PVC) act as devices to introduce poorly soluble drugs in an aqueous surrounding such as the bloodstream [57].

Chitosan hydrogels with high strength and strongly woven framework fibers based on nanofibrous architecture can be synthesized by dissolving chitosan in alkaline solution. This strong hydrogel shows remarkable biocompatibility, pH sensitivity, and smart controlled drug release properties [58].

3.4 Applications of Alginate-Based Hydrogels

Alginate hydrogels serve as biomaterials. They are extremely diverse and adapt to the environment in which they are employed. The alginate gel application in the near

future is most likely to be the growth factor distribution and good tuning of the three-dimensional distribution and sequential kinetics of factor release. Protein factors can either be directly inserted into the polymer or delivered indirectly in the form of plasmid DNA that can transfect cells adjacent to the gel [94].

Alginate gels can also be potentially used as a model extracellular matrix (ECM), specifically when associated with the new fluorescence resonance energy transfer (FRET) techniques which allow the imaging of ligand clustering, the pattern of strains, and cell-generated stress field calculations [95].

The alginate hydrogels also act as bulking agents. Alginate gels with appropriate properties are being used in tissue bulking entities. The incorporation of adipocytes into these gels, enhance their bulking property [96]. A highly targeted drug release with limited exposure to tissues is very significant. Alginate hydrogels are extensively used for the persistent and restricted delivery of conventional low molecular weight drugs [97].

3.5 Application of Hemicellulose-Based Hydrogels

The hemicellulose hydrogels are used in different fields of science and are immensely important. A hemicellulose hydrogel which is pH-sensitive and biodegradable is prepared by the grafting of acrylic acid into HC. Such hydrogels can be employed as a carrier for oral drugs. These HC hydrogels can be loaded with drugs and processed further into tablets. As the swelling of such loaded hydrogels differs with varying pH values, they can prevent the release of the drug in the human digestive tract; similarly, the release of drug can be controlled in the small intestine or other organs [75].

The films of xylan (a form of HC) can be transformed into hydrogels when immersed in water. They have liquid transportation properties because of the microporous structure and hence are employed for the transportation of the liquid [76]. *O*-acetyl galactoglucomannan is a form of hemicellulose and is employed in the production of cationic HC- based hydrogels. These hydrogels are useful in removing the metallic ions from the aqueous solutions particularly arsenic and chromium [77].

Macroporous hemicellulose-based hydrogels also remove heavy metals from the aqueous solution by the adsorption method. These gels can be reused up to eight cycles. Such gels are used for the removal of zinc, lead, and cadmium ions. The recovery efficiency is also very high; it is 98.9%, 99.1%, and 99.0% for Pb^{2+}, Zn^{2+}, and Cd^{2+}, respectively, in the first cycle and in the eighth cycle. However, the efficiency decreases and comes to 96.7%, 96.4%, and 97.6% for Pb^{2+}, Zn^{2+}, and Cd^{2+}, respectively [78].

The hydrogels prepared by freeze–thaw method are non-toxic and bio-compatible. They have vital applications in the tissue developing and modification technology. Because of their crystalline structure, they are employed in biomaterials synthesis [79].

4 Conclusion

This chapter presents the review on carbohydrate-based hydrogels. The carbohydrates such as cellulose, hyaluronic acid, chitosan, and alginate are discussed in this study. Synthesis techniques and processes are extremely important for required applications. Here, the synthesis mechanisms such as atomization, polymerization, physical and chemical cross-linking, solution polymerization, freeze–thaw method, grafting, and polymerization by irradiation have been discussed. Each type of synthesis and substrate material leads to a different kind of application. The study in this chapter briefly highlights their application in various fields. They are widely used in tissue engineering, for water purification and for removal of heavy metal ions, as a carrier for different types of drug delivery and for cartilage repairing, and are utilized as anti-adhesive substances in postsurgical procedures.

5 Future Scope

Biopolymers are very useful and have been serving the need of scientists across the world. They are being comprehensively investigated for possible application in various fields. They are employed in various areas of life, such as in bio-medical sciences and water treatment. However, there are yet several areas in which these hydrogels can perform wonders such as in gas purification, dye removal from textile water, barrier against various hazardous material, heat and sound absorbers, artificial organ development, antifungal/antibacterial bandages, repairing of joints and cartilage, development of artificial muscles, etc. In order to get more benefit from the hydrogels, researchers must explore their characteristic potential and properties.

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Smart Biopolymer Hydrogels Developments for Biotechnological Applications

51

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Contents

Abstract

Natural-based polyelectrolytes, especially polysaccharides, have received increasing attention in biomedical and pharmaceutical fields due to biodegradability, biocompatibility, natural abundance, unique chemical structures and physicochemical/biological properties, and the ability to form hydrogels. A class of hydrogel which changes its shape, surface characteristics, and solubility or undergoes formation of an intricate molecular self-assembly or phase or conformational transition with external stimuli, such as pH, temperature, ionic strength, solvent composition, the presence of salt ions, light, or electric field,

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is considered to be a "smart" hydrogel (also referred to as stimuli-responsive hydrogel). These kinds of hydrogels have been proposed for biotechnological applications, such as the delivery of therapeutic agents, tissue engineering, flow control, sensors/diagnostic devices, and actuators. Among these hydrogels, alginate and chitosan biopolymers have been categorized as pH-sensitive, temperature-sensitive, as well as dual pH- and temperature-responsive hydrogels and were discussed in this chapter.

Keywords
Biopolymer · Smart hydrogel · Alginate · Chitosan · pH sensitivity · Temperature sensitivity

1 Introduction

Biopolymeric hydrogels are three-dimensional networked structures, able to swell and hold the volume of the sorbed aqueous solution in their networks. These networks are prevented from dissolving due to the chemical or physical bonds formed between the polymer chains [1, 2]. Nowadays, hydrogels still have much increasing interest from scientists, and enormous developments have been made regarding their formulations and biotechnological applications [3–5]. Hydrogels are classified according to their monomeric composition based on the method of preparation, namely, homopolymeric hydrogels, copolymeric hydrogels, and interpenetrating polymeric hydrogels [6]. Moreover, hydrogels can be classified as either neutral, anionic, cationic, or ampholytic hydrogel based on the presence of ionic charges on the monomer. According to the physical nature, hydrogels could be classified into amorphous or semi-crystalline hydrogels [7–9]. Hydrogels can also be divided into two clusters based on their natural or synthetic origins [10]. Hydrogel-based natural polymers include polysaccharides such as cellulose, alginate, and chitosan, and proteins such as gelatin and collagen. These hydrogels have many beneficial features, such as biodegradability, excellent biocompatibility, and low toxicity [11, 12]. A new class of biopolymeric hydrogels has a great response to various environmental conditions called "smart hydrogels" and will be discussed in details in the following sections.

2 Smart Hydrogels

Smart "intelligent" hydrogels are stimuli-responsive polymers that may undergo reversible volume phase transitions or sol–gel phase transitions upon changes in the environmental condition such as pH, temperature, electric field, solvent composition, the presence of salt ions, and light [13, 14] as shown in Fig. 1. Due to their excellent unique properties, these smart hydrogels play an important role in several biotechnological applications, and the most significant systems from the medical and pharmaceutical point of view are those sensitive to pH or temperature [15, 16].

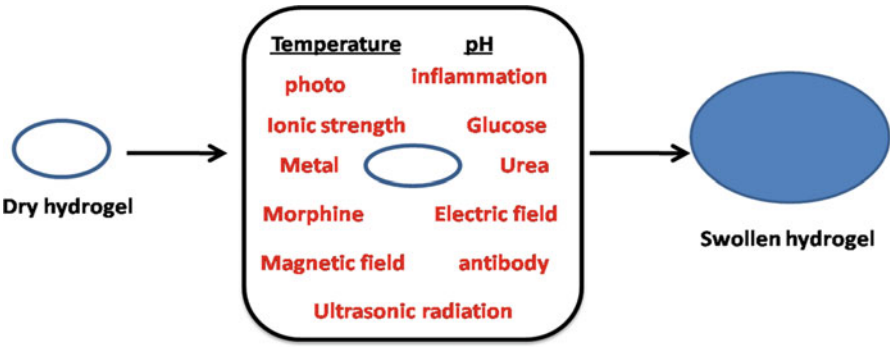

Fig. 1 Response of smart hydrogel to different stimuli environmental conditions

2.1 pH-Sensitive Hydrogels

Commonly, the pH-sensitive hydrogel consists of ionizable acidic or basic pendant groups such as carboxylic acid, sulfonic acid, or amines. Therefore, when the pH of the external solution is above the pK_a value of the acidic pendant groups, the hydrogel becomes polyanionic, while below the pK_b of the basic pendant groups, the polymeric hydrogel is polycationic. It has been reported that the pendant acidic or basic groups that either accept or release protons in response to changes in environmental pH [17]. Hydrogels which have ionizable groups are known as polyelectrolytes; these acidic or basic groups on polyelectrolytes undergo ionization just like acidic or basic groups of monoacidic or monobasic. Nevertheless, complete ionization on polyelectrolytes is more difficult due to electrostatic effects. The hydrogel swelling will be enhanced as the external pH increases in the case of weakly acidic (anionic) groups and decreases if the hydrogel contains weakly basic (cationic) groups [18, 19]. It has been stated that the pH range where a reversible phase transition arises can be mostly controlled by two approaches:

(A) Choosing the ionizable moiety with a pK_a similar to the desired pH range, where for any desired application, the suitable selection between polyacid and polybase should be considered.
(B) Introducing hydrophobic groups into the polymer backbone and controlling their nature, amount, and distribution. This can offer a more compact conformation in the uncharged state and a more suspect phase transition. The hydrophobicity can be controlled by a copolymerization process for the hydrophilic ionizable monomers with other more hydrophobic monomers with or without pH-sensitive moieties, such as methyl methacrylate (MMA) and 2-hydroxyethyl methacrylate (HEMA).

Examples of pH-sensitive hydrogels with anionic groups are polyacrylic acid (PAA), poly methacrylic acid (PMAA), carboxymethyl cellulose (CMC), and alginate (Alg), while examples of cationic polyelectrolytes are poly (*N, N*-

dialkylaminoethyl methacrylates), polyethyleneimine (PEI), and chitosan (CS) [20, 21]. pH-sensitive hydrogels have been widely studied in the field of drug delivery systems in the gastrointestinal tract (GI tract) for site-specific delivery and have been developed as carriers for low-molecular-weight protein drugs as well as protein concentration [22].

The notion of using pH as a trigger to drug release at the internal site is based on changing pH down the GI tract. pH and protease labile protein therapeutics can be protected by the collapsed/compact gel matrix in the gastric environment (pH~1.2) while being released in the intestinal lumens (pH~7.8) through matrix swelling or erosion [23]. In the tissue engineering application, pH-sensitive hydrogels which include carboxylate anions on the hydrophilic surface could improve the biocompatibility via minimizing immunogenic effects and imitate the characteristics of the cell surface in vertebrates [24].

2.2 Temperature-Sensitive Hydrogels

Temperature-sensitive hydrogels can change their microstructure properties responding to the difference in temperature (thermo-stimuli-responsive). This kind of smart hydrogels is considered as the most secure polymers for drug delivery as well as biomedical applications [25]. The sensitivity of hydrogels to environmental temperature is helpful as the temperature is the main reason for their gelation with no chemical or physical treatment. The main feature of thermosensitive hydrogels is the tunable solubility caused by changes happened in the hydrophilic–hydrophobic character of smart hydrogel via increasing the induced temperature [26]. The development of temperature-sensitive hydrogels as will be briefly explained can be divided into three major working mechanisms [27], shape-memory materials, liquid crystalline materials, and responsive polymer solution, which considered the popular classes of thermosensitive polymers [28].

Additionally, hydrogels have been engineered to respond to varying temperature (responsive hydrogels) to undergo a volume phase transition for drug delivery and biomaterial applications [29]. The technique of the volume phase transition occurs when the network transitions between a solvent-swollen network and a hydrophobic collapsed state via the difference in mixture salvation [30] as shown in Fig. 2, with an example of thermosensitive chitosan hydrogel. The process of transition from solution to gel is often known as the sol–gel transition. The separation from solution and solidification for some hydrogels may be exhibited above the specific temperature [31]. The lower critical solution temperature (LCST) is considered as threshold temperature for hydrogels. It is well known that polymers have two behaviors where they are soluble below LCST while they become hydrophobic and insoluble above LCST when the gel can form [32]. On the contrary, hydrogels that can be formed upon cooling polymer solution have an upper critical solution temperature (UCST) [14].

Three different types of thermosensitive hydrogels are stated as follows.

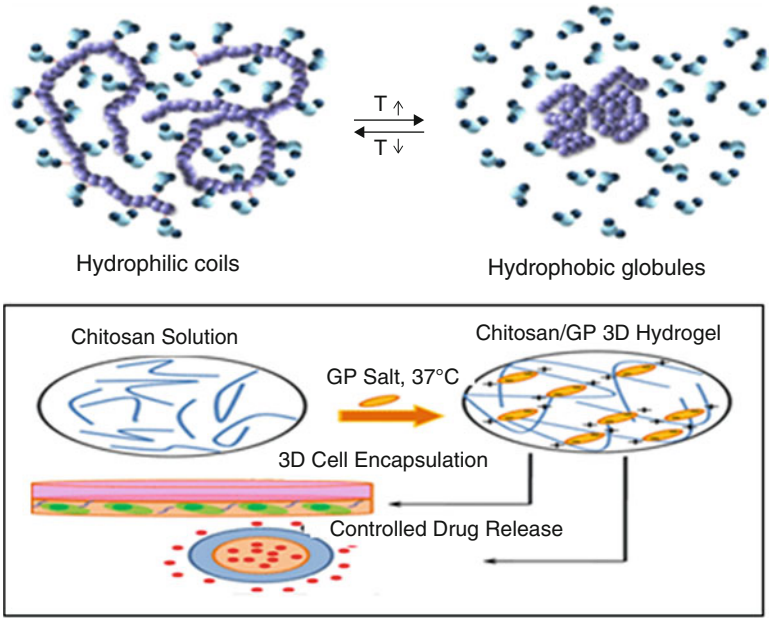

Fig. 2 The behavior of smart hydrogels under a thermo-stimuli system with an example of chitosan 3D hydrogel [32]

2.2.1 Negative Temperature-Sensitive Hydrogels

This type is going through an LCST transition in water showing solubility in water at a low-temperature value, while increasing temperature, the phase separation appears [30]. From the thermodynamic point of view, this obtains the Gibbs free energy $\Delta G = \Delta H \updownarrow + T\Delta S$ of polymer dissolution in water that is negative at lower temperatures and converts to positive upon increasing temperature. This behavior occurs when the enthalpy (ΔH) is negative, and the entropy (ΔS) also becomes negative when water lost entropy and hydrated to the hydrogel networks. The LCST transition is a completely reversible supportive (de)hydration process providing contact with sharp reversible temperature-induced polymer phase transitions [33]. The thermosensitive hydrogels are used as drug delivery system; the main reason for its use is the fact that body or body site temperature may change upon fever or local infections or diseases, and a drug may be released as a result of such trigger if the LCST of the material is close to body temperature. A hydrophilic drug is integrated into the swollen gel; when the temperature decreases below the LCTS, the diffusivity increases and the drug can be released [34].

2.2.2 Positive Temperature-Sensitive Hydrogels

They are an upper critical solution temperature (UCST) that can be contracted upon cooling below the UCST. To summarize the UCST behavior, ΔH for super molecules association of the polymer chains should be introduced in the Gibbs free

energy equation [35]. Hydrogel networks with strong associative interactions break upon network dissolution, and this leaves the hydrogel insoluble if this loss of energy is larger than the gain in energy upon dissolution [36]. However, the hydrogel network interaction strength decreases with increasing temperature causing dominant the hydration term and leading to the dissolution. The hydrogel tends to be very hydrophilic avoiding its potential LCST transition that is lower than UCST transition that exhibits complete insolubility. It can be concluded that the swelling happens in higher temperature and the release occurs at low temperature [37].

2.2.3 Revisable Temperature-Sensitive Hydrogel

If the polymer chains in hydrogels are not covalently cross-linked, temperature-sensitive hydrogels may undergo sol–gel phase transitions, instead of swelling–shrinking transitions. The thermally reversible gels with inverse temperature dependence become sol at higher temperatures. Polymers that show this type of behavior are block copolymers of PEO and PPO [38].

Temperature-responsive hydrogels can be simply applied in vitro and in vivo conditions [39, 40]. Besides, body/body site temperature could be varied upon fever or diseases or local infections. Consequently, the drug may be released when the LCST of the material is close to body temperature. There are diverse methods to introduce therapeutic agents into these systems either by swelling the dry materials in the drug solution or by synthesizing the hydrogel using a mixture of monomer or polymer together with the drug. Poly(*N*-isopropyl acrylamide), PNIPAAM, has been the most used macromolecule in temperature-sensitive hydrogels. Temperature change in PNIPAAM depends on the existence of low LCST (a phenomenon that is thermodynamically related to that causing temperature-induced protein folding). Conversely, a reversible conformational transition may occur above LCTS [41]. In this context, Serres [42] and Ganorkar [43] and their groups fabricated an intestinal delivery of human calcitonin from Poly(NIPAM-co-BMA-co-AAc). Moreover, Kim demonstrated the insulin delivery [25]. The grouping of the hydrophobic butyl methacrylate (BMA) and not ionized acrylic acid (AAc) especially at lower pH inhibits beads disintegration in the acidic medium of the stomach. In contrast, beads start to disintegrate at higher pH owing to solubilization caused by the now ionized acrylic acid. Recently, Chilkoti and his research team [44, 45] reviewed the field of elastin-like polypeptides via designing a double-responsive doxorubicin–polypeptide conjugate for cancer therapy. The conjugated polymer can be used for passive targeting by EPR effect [46]. Besides, the faintly elevated temperature of the tumor is enough to tolerate a phase transition due to the adaptation of the LCST behavior of these developed polymers. Hudson studied the effect of silk-fibroin-interpenetrating polymer networks (SFIPNs) on swelling/deswelling kinetics and rheological properties of PNIPAAM hydrogels. It was found that the formed IPNs hydrogel illustrate identical NaCl concentration and volume phase transition temperature as pure PNIPAAM hydrogels. Additionally, synthetic PNIPAAM/SF IPNs improved the deswelling kinetics while keeping the swelling rate of PNIPAAM. Alternatively, an introduction of SF with beta-sheet crystalline structures could

decrease the effect of the skin layer and enhance mechanical characteristics of the IPN hydrogel compared to pure PNIPAAM hydrogels.

3 Alginate-Based Hydrogels

Alginate (Alg) is a low-toxic water-soluble anionic biopolymer, extracted from the cell walls of brown algae with a relatively low cost [47, 48]. Alginate consists of 1,4-linked d-mannuronic acid and 1,4-linked l-guluronic acid (M and G blocks) arranged linearly in a pyranose form as shown in Fig. 3 [49]. It is widely successfully used in various industrial, biomedical, and pharmaceutical applications [50, 51]. Alginate has numerous unique properties such as excellent mucoadhesive property, a quite inert aqueous environment within the matrix, and a mild room temperature encapsulation process free of organic solvent. As well a high gel porosity allows for high diffusion rates of macromolecules and has the ability for dissolution and biodegradation of the system under normal physiological conditions [33, 52].

3.1 pH Sensitivity of Alginate

Indeed, alginate has one carboxylic acid in its monomer and pK_a of alginate differs somewhat only from those of the monomeric residues (3.38 and 3.65 for mannuronic and guluronic acid, respectively). Alginate is able to shrink at low pH, and the encapsulated drugs are not released, where the hydrated sodium alginate is converted into a porous, insoluble so-called alginic acid skin. Once passed into the higher pH, the alginic acid skin is converted to a soluble viscous layer. On the other hand, at the basic conditions (pH 8–12), alginate is degraded by β-alkoxyelimination and the rate increases linearly with time and increases in proportion to OH^- concentration, while alginate is stable at the pH range 7–8 [33, 53]. pH sensitivity of alginate can be exploited to alter the drug release profiles. Nevertheless, the fast dissolution of alginate in the higher pH ranges can result in burst release of protein drugs. Omer and his co-authors developed a new chemically modified alginate microcapsule to

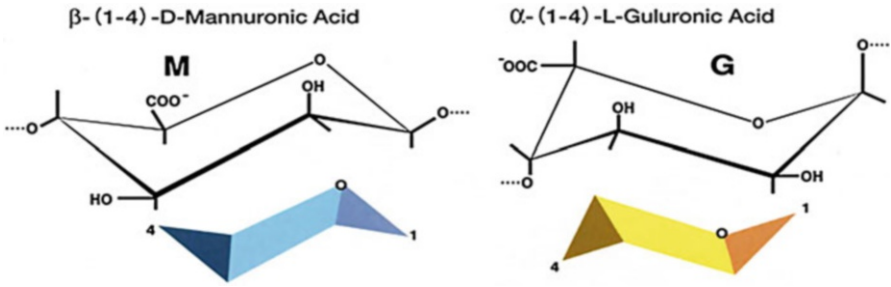

Fig. 3 Chemical structure of alginate biopolymer

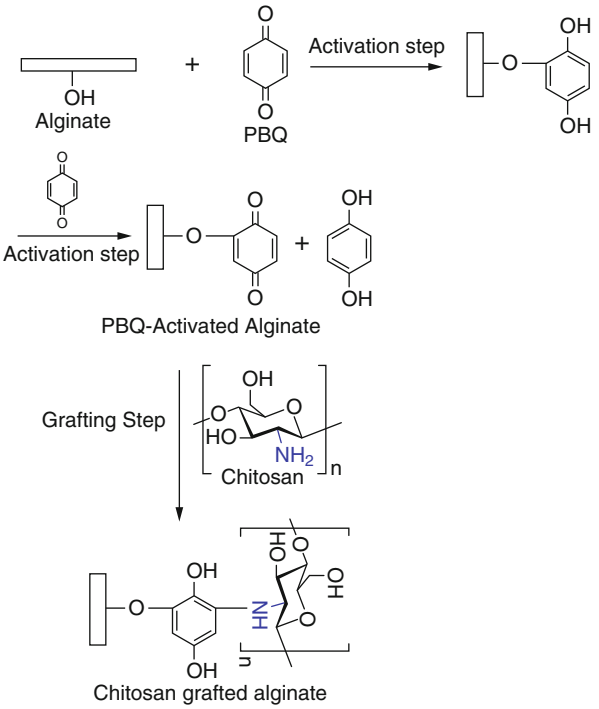

Fig. 4 Synthesis of chitosan-grafted alginate pH-sensitive hydrogels

overcome these drawbacks as well as enhance the pH sensitivity of alginate in GI tract for the delivery of protein drugs (bovine serum albumin, BSA). The modification process was achieved by click chitosan grafting on the surface of alginate using p-benzoquinone (pBQ) as a covalently coupling agent as investigated in Fig. 4, and by a coating of alginate microcapsules by aminated chitosan layers. Therefore, many modifications in the physicochemical properties are needed for the prolonged controlled release of protein drugs. Results showed that alginate-grafted chitosan microcapsules exhibited high swelling degree and were much stable at the acidic conditions, while maximum swelling degree was observed at pH range 6.8–7.4 [54–56].

A semi-IPN superabsorbent hydrogel based on sodium alginate-*g*-poly (sodium acrylate) (NaAlg-*g*-PNaA) network and linear polyvinylpyrrolidone (PVP) was prepared by simple free radical polymerization in the presence of ammonium persulfate (APS) as initiator and *N*, *N*-methylene-*bis*-acrylamide (MBA) as a cross-linker. In this article, Wang revealed that the introduction of PVP into NaAlg-*g*-PNaA network and the formation of semi-IPN structure significantly enhanced water absorption and swelling rate of the formed hydrogel. Besides, the hydrogel possesses outstanding sensitivity to external pH stimulus and shows reversible on/off switching swelling properties [57]. On the other hand, Hua and his co-authors prepared a sodium alginate/poly(vinyl alcohol) (SA/PVA) hydrogel beads via Ca^{2+} cross-linking and freeze–thawing (FT) cycle approaches. They aimed

to improve the drug (diclofenac sodium) entrapment efficiency and enhance the swelling characteristics of drug delivery system [58]. It was demonstrated that both swelling and degradation of the developed beads were greatly influenced by pH of the test medium and PVA content. Also, the FT process has a positive effect on drug entrapment efficiency and swelling behaviors besides the reduction in release rate providing a superficial and efficient method to advance the drug delivery system. Additionally, George and his co-authors developed a pH-sensitive alginate guar gum hydrogel cross-linked with glutaraldehyde (GA) for the controlled delivery of protein drugs (BSA) in mild conditions and aqueous medium [59]. The freeze-dried hydrogels showed proper swelling ratios (∼8.5) for drug release in the simulated intestinal environment, while the protein delivery from the tested hydrogels increased from 20–90% by increasing pH from 1.2 to 7.4. It was also noted that the presence of guar gum and GA increases the entrapment efficiency and inhibits the fast alginate dissolution at higher pH of the intestine which ensures the controlled release of the entrapped drug. More recently, Sarkar demonstrated the design of carbon quantum dots (CQDs) tailored calcium alginate (CA) hydrogel films (CA/CQD) to control the delivery of glycopeptides antibiotic vancomycin in the gastrointestinal tract (GI) [60]. Results verified that drug-loading capacity of CA/CQDs films is increased to 89% compared to 38% for transparent CA film by the addition of CQD, whereas the vancomycin uptake capacity is increased to 96% with β-cyclodextrin (β-CD). Also, the release of vancomycin through CA/CQD is more distinct at pH 1.5 that is close to the pH of the stomach where the release rate of vancomycin is decreased to 56% in 120 h at the same pH with β-CD. These data confirmed the possible applicability of this film as drug delivery vehicle for controlled release of vancomycin into the stomach medium.

Moreover, Manatunga and his team [61] developed a pH-responsive drug carrier system. A novel pH-sensitive sodium alginate (NaAlg) and hydroxyapatite (HA) bilayers are coated with iron oxide nanoparticle (IONP) composite (IONP/HAp-NaAlg) via the co-precipitation technique for the controlled release of anticancer drugs. In this study, both loading capacity and efficiency of curcumin and 6-gingerol were evaluated. In vitro, drug delivery behavior and the mechanism of drug release were also studied. Moreover, Chen and his group prepared alginate (Alg)-grafted anisotropic silica (SiO_2-x) via the Ugi reaction [62]. Three liquids of paraffin were examined in water emulsions compared to pristine SiO_2-x. These emulsions became more stable as pH varied from 2.0 to 6.2. On the contrary, when the emulsion pH was 9.0, the emulsion stability dropped off due to the consequent reduction in particle charge. Λ-cyhalothrin drug was entrenched in the emulsions and describable by the Weibull model. A sustained release assay established that increasing emulsion pH from 3.0 to 8.0 diminishes cumulative drug discharge from 99.7% to 13.5%. This result designated that the synthesized emulsion is a pH-triggered drug delivery system. A drug targeting magnetic bead containing $CoFe_2O_4$ nanoparticles, sodium alginate (Alg), and chlorpheniramine maleate (CPAM) were synthesized in the presence of Ca^{2+} ions to obtain ionic cross-linked magnetic hydrogel beads [63]. Amiri and his group illustrated that the swelling rates of the formed beads showed pH-dependent character with maximum water absorption capacity at pH 7.4.

However, in vitro release of the magnetic beads exhibited unusual behavior on the subject of nanoparticles concentration and Alg content. Furthermore, biocompatibilities of the CFO nanoparticles and MCFO/Alg beads are confirmed through cytotoxicity examination using MTT assay on U87 cell lines.

A novel pH-sensitive hydrogel based on l-arginine-grafted alginate (Arg-g-Alg) hydrogel beads was synthesized and employed as a new carrier for protein delivery (BSA) in specific pH media [64]. Nonetheless, the swelling trend of Arg-g-Alg beads was estimated as a function of pH and compared with original calcium alginate beads. Thus, it was mentioned that release profile behavior was greatly improved owing to the grafting of Alg particularly in acidic media.

3.2 Temperature Sensitivity of Alginate

In recent years, alginate showed unique characteristics as biocompatibility, biodegradability, and biological functions as well as the stimuli-responsive properties. De Moura and his research group prepared a thermosensitive porous hydrogel composed of IPN of Ca^{2+} alginate and PNIPAAM by cross-linking Na^{+} alginate with Ca^{2+} ions inside PNIPAAM networks. It was verified that higher strength is achieved, while IPN hydrogels present small pore size and when the temperature is raised [65]. A novel thermal-responsive membrane containing IPNs of alginate Ca^{2+} and PNIPAAM was synthesized by Guilherme and his research team. The data revealed that the shrinking rate was depending on heating rates. Further, this phenomenon is faster and highly effective in IPN gel containing lesser amount of Ca^{2+} alginate [66]. Also, semi-IPN combining matrix of Ca^{2+} alginate with PNIPAAM was fabricated and characterized. It was reported that the incidence of PNIPAAM chains inside semi-IPN hydrogel alters water affinity compared to pure Ca^{2+} alginate hydrogel. Moreover, no shrinking of semi-IPN hydrogel was observed during the phase separation when water uptake decreases above 32 °C [67]. Anti-inflammatory agents were loaded in chitosan /alginate microspheres to set up solid dosages form for colon-targeting. Lipophilic drugs such as prednisolone were laden in mucoadhesive chitosan-coated alginate microparticles via single- or double-step particle formation and coating technique. Higher mucoadhesives were obtained by one-step method compared to those prepared by two-step method [68].

In another research study, an amino-terminated NIPAAM copolymer (PNIPAAM-NH_2) was covalently coupled with -COOH present in alginate chains involving water-soluble carbodiimide chemistry. The temperature dependence of PNIPAAM-g-alginate hydrogels was obvious from a noticeable decrease in the swelling degree above 32 °C. Release behavior from calcium-cross-linked alginate-g-poly-NIPAAM beads was also demonstrated using blue dextran as a model drug. The release rate of blue dextran from the cross-linked beads was advanced at 40 °C than at 25 °C; this difference was more measurable when PNIPAAM content increased. Further, the release rate should be low as the beads porosity reduced by the expanded PNIPAAM under the LCST. In contrast, the pores were opened above the LCST leading to faster release rates [69, 70].

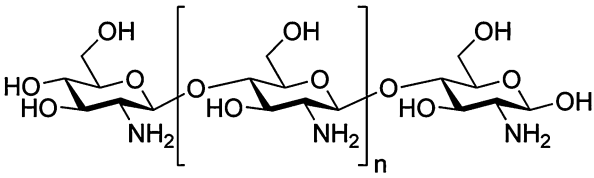

Fig. 5 Chemical structure of chitosan biopolymer

4 Chitosan-Based Hydrogels

Chitosan (CS) is a natural amino functionalized polysaccharide and consists of a copolymer of β-[1→4]-linked 2-acetamido-2-deoxy-d glucopyranose and 2-amino-2-2-deoxy-d-glucopyranose as shown in Fig. 5 [71]. Chitosan has an excellent advantage and specific characteristic properties such as low toxicity, antibacterial activity, antifungal activity, antioxidant activity, biodegradability, biocompatibility, wound healing, and film-forming ability. Amine and hydroxyl groups along with chitosan backbone exhibit its hydrophilic character that is utilized in biomedical and pharmaceutical industries as a component of hydrogel [72–75].

4.1 pH Sensitivity of Chitosan

Undeniably, chitosan can be dissolved in the acidic medium below pH 6.5, and this required ensuring the protonation of the present primary positive amine groups on its backbone. These positive charges increase the repulsion forces between the different chitosan chains and simplifying their solubilization. Furthermore, chitosan exhibits a pH-sensitive behavior resulting from a large number of amino groups [76] as shown in Fig. 6. This property is useful in case of the delivery of chemical drugs to the stomach. Conversely, this property is limited in case of delivery of protein drugs to the intestine, and this is due to the dissolution of the chitosan matrix in the stomach. Several physicochemical modifications have been applied to improve the stability of chitosan in the stomach and controlled delivery of proteins [77]. Polyelectrolyte complexes developed from chitosan and anionic polyelectrolytes through electrostatic interaction can efficiently protect the encapsulated agents from gastric degradation and release them in response to the high pH of the intestine [78]. Cross-linking of chitosan is the straightforward and efficient approach to improve the resistance to chemical and long-term gastric degradation [79].

Chitosan–alginate polyelectrolyte complex (PEC) was formed at the optimum pH via ionic interaction (Fig. 7) between the positively charged amine groups of chitosan and the negatively charged carboxylic groups of alginate [80]. This PEC being a pH-sensitive hydrogel and has been deliberate for the development of oral delivery of protein drugs. It has been reported that PEC formed from chitosan and synthetic polymers such as polyacrylic acid, poly(lactic-co-glycolic acid) (PLGA), and poly(g-glutamic acid) could be applied as pH-sensitive PEC for protein delivery [81–83].

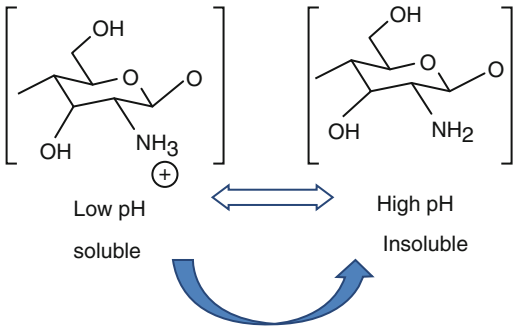

Fig. 6 pH sensitivity of chitosan biopolymer

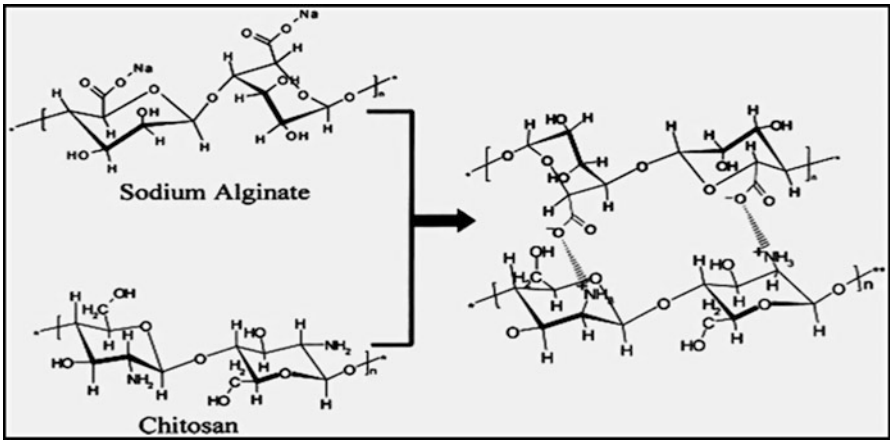

Fig. 7 Ionic interaction between alginate and chitosan pH-sensitive PEC

Porous chitosan microspheres suitable for the delivery of antigen were prepared by using a wet phase-inversion method by Mi and other researchers [84]. The results showed that the pore structure of the chitosan microsphere could be modified by the change of pH value of the coagulation medium, which is the aqueous solution of TPP. The high porosity of chitosan microsphere with an open porous structure on its surface was prepared by coagulation in TPP aqueous solution of pH 8.9. The porous chitosan microspheres were modified chemically with reagents to introduce carboxyl, hydrophobic acyl, and quaternary ammonium groups. The antigen of Newcastle disease (ND) vaccine was immobilized into the pores of porous chitosan microspheres, and the adsorbed antigen was assayed by the hemoglobin aggregation analytical method. Sustained release of ND vaccine's antigen was studied by an adsorption–desorption release test. The chemical modification of the porous chitosan microspheres had a strong influence on the adsorption efficiency or release rates of the antigen investigated. The porous microspheres had higher adsorption efficiency and the slower release rate of the antigen when modified chemically with 3-chloro-2-hydroxyl propyl trimethyl ammonium chloride.

Conversely, Song [85] attempted to prepare water-insoluble conjugates of mitomycin C (MMC) with succinyl-chitosan. MMC, succinyl-chitosan, and water-soluble carbodiimide (EDC) were mixed in water for 45 min after adjusting to pH 5.0, because the MMC content of the conjugates was lowered with the increase in the pH in the reaction medium. Moreover, Onishi [86] prepared the cross-linked conjugate microparticles of succinyl-chitosan with MMC having an adequate size (0.2–3 mm) for liver targeting. The release characteristics of succinyl-chitosan-MMC exhibited mono-exponential liberation of MMC at pH 7.4 [87, 88]. Another study reported that cross-linked conjugate microparticles of succinyl-chitosan with MMC exhibited a faster release as compared with succinyl-chitosan-MMC. These differences may be attributed to the stiffness of the particles (tight or loose) rather than the binding between succinyl-chitosan and MMC because the liberation of MMC forms the conjugates of MMC with succinyl-chitosan that depends on the pH in the medium [89, 90].

4.2 Temperature Sensitivity of Chitosan

Wu and his research group [91] designed and prepared a new thermosensitive hydrogel simply by mixing *N*-[(2-hydroxy-3-trimethylammonium) propyl] chitosan chloride (HTCC) and poly(ethylene glycol) (PEG) with the addition of small amount of α-β-glycerophosphate (α-β-GP). The obtained hydrogel was evaluated for nasal drug delivery systems for peptide/or protein drug that used chronically, by dropping or spraying easily into the nasal cavity and transform to hydrogel at 37 °C. In an animal study, the insulin-entrapped hydrogel formula was found to reduce the blood glucose concentration apparently (40–50%) of its initial concentration within 4–5 h once running, without any perceptible cytotoxicity.

A novel injectable in situ thermoresponsive chitosan-β-glycerophosphate hydrogel has been lately proposed for tissue repair and drug delivery systems [92]. This system can maintain the macromolecules release from numerous hours to a few days. Hence, to a solution of chitosan-β-glycerophosphate, liposomes were added, and their outcomes on the system viscoelastic properties and the rate of kinetics release of encapsulated carboxyfluorescein were investigated. It was found that the occurrence of liposomes faintly improved both gelation rate and strength and strongly affects the release rate with an insignificant effect on kinetics when lipid with high phase transition temperature was used. Lorenzo and his team group [93] stated the anionic drug affinity and released behavior of PNIPAAM/chitosan IPNs. A notable high affinity for the anionic drug (diclofenac) was remarked against the pure PNIPAAM hydrogel with the ability to sustain the drug release for 48 h at pH 8 of phosphate buffer. These conditions cause delaying in drug diffusivity by collapsed PNIPAAM networks at 37 °C. Further, the IPN formulations with poorer chitosan post-cross-linking degree showed the preferred temperature-sensitive release. The release of poly(chitosan-co-NIPAAM)/poly (methacrylic acid-co-methyl methacrylic acid) particles was investigated with caffeine to study their applicability in the targeting drug field. The results confirmed that drug might be

merged inside the copolymer using swelling process and effectively protected from releasing in phosphate buffer solution at 37 °C [94]. In the protein conjugation experiments, the conjugated bovine serum albumin BSA amount on the copolymer surface was influenced by many factors including the size of swollen particles, their hydrophobic characteristics, and the amount of -COOH groups on the particle surface. Thus, the degree of conjugation increased at either 37 or 25 °C with increasing the surface -COOH groups and the particles sizes with a considerable increase at 25 °C.

More studies by Bhattarai and his group [95] have been conducted to synthesize an injectable thermo-hydrogel based on poly(ethylene glycol) (PEG)-g-chitosan for drug release in vitro using BSA as a protein model. The resultant copolymer solution becomes injectable at a lower temperature when the amount of PEG grafted to chitosan chains was >40 by weight and transformed to the semisolid state at the body temperature. During the release experiment, a steady linear release of protein from the resulted hydrogel was attained for a period of 70 h. What is more, cross-linking the hydrogel with genipin in situ achieves the extended quasi-linear release of protein up to 40 days.

5 Dual Stimuli-Responsive Hydrogels

A series of double-responsive systems have been reported. Double- or multi-responsive systems can be renowned according to polymer architecture. Random copolymers are used to adapt the transition point depending on two independent parameters, e.g., pH and temperature. Due to the pH-sensitive characters of polysaccharides, a grouping of these biopolymers with thermoresponsive materials will produce the dual stimuli-responsive polymeric gel for using as delivery vehicles responding to localized conditions of pH and temperature in human bodies. Shi and his team [96] prepared a semi-interpenetrating polymer network hydrogel beads (semi-IPN), based on calcium alginate (Ca-alginate) and PNIPAAM, for a pH/temperature-sensitive drug delivery system. The LCST measured by DSC was around 33–34 °C, showing the independent character of the composition, while the equilibrium swelling of the beads evidently verified the independent pH- and temperature-responsive nature of the synthetic materials. Also, the drug release behavior of indomethacin incorporated into these beads was reported as a function of pH and temperature as well as PNIPAAM content (Alg-N-isopropyl acrylamide). Both thermal and photoresponsive PNIPAAM endoglucanase conjugates were developed by Hoffman [97, 98] using site-specific conjugation strategy. Under irradiation at 350 nm, these endoglucanase becomes inactive for glycoside hydrolysis.

Peppas and his team [99] prepared an anionic pH-sensitive hydrogel for calcitonin entrapment. As well as in thermal stimulus, only physically entrapped proteins can be released (thermo- and pH-responsive polymers in drug delivery). Chitosan-coated alginate beads containing PNIPAAM were prepared by Shi and his co-authors with enhanced encapsulation efficiency (84%) than that of the uncoated ones (74%) and slow release profile rate [100]. Grafting copolymerization of

different acrylic monomers onto polymeric backbones having hydroxyl groups by using ceric ammonium nitrate (CAN) was studied in many articles [101, 102]. Lately, NIPAAM monomer was grafted onto chitosan using CAN as initiator producing a copolymer with thermally reversible hydrogel character exhibits an LCST around 32 °C in aqueous solutions. Additionally, the swelling ratios were higher at pH 4 than at pH 7 [103–105]. The equilibrium water content of the resulted hydrogels significantly decreased above the LCST of PNIPAAM compared with that at 25 °C. Likewise, nontoxic and biocompatible properties were approved by in vitro study [106]. On the other hand, Verestiuc and his group have conducted the free radical polymerization for preparing semi-IPNs of NIPAAM onto chitosan using tetraethyleneglycoldiacrylate (TEGDA) as a cross-linking agent [107]. It was noticeable that the phase transition temperature of the interpenetrated hydrogels becomes lesser as the content of chitosan and cross-linking density increased. Furthermore, incorporating chitosan into the semi-IPN structure-induced pronounced pH sensitivity. On another work, a full IPN hydrogel was established via a direct chemical combination of methylene-bis-acrylamide (MBAM) cross-linked PNIPAAM network with formaldehyde cross-linked chitosan chains [108]. Including the extractability of PNIPAAM within the IPN hydrogel structure affects the swelling rates in aqueous solutions (water and/or ethanol) and phase transition behavior. Also, the microstructure of the fully prepared IPN hydrogels is quite dissimilar from those of the semi-IPN hydrogel with at least 4–5 °C LCST that is greater than that of the corresponding semi-IPN hydrogel. Grafting of natural polymers with vinyl monomers using the irradiation method has received much attention in the recent years. It was reported that coupling chitosan with maleic anhydride produced maleilated chitosan [109]. And both pH and temperature influence the swelling percentage of mutilated chitosan-g-PNIPAAM. Copolymers with higher grafting ratios at lower temperatures (<32 °C) showed the highest optical transmittance. As well increasing the grafting percent pronounces phase transition trend. Irradiation technique was also used extensively for grafting PNIPAAM onto chitosan, alginate, and cellulose [110, 111]. The common in all these studies is grafting percentage and efficiency were increased by the increase in monomer concentrations and total irradiation dose. In the case of chitosan-g-PNIPAAM hydrogels, the swelling ratios improved by increasing the amount of grafted monomers where it reduced the rise in pH value and the LCST was around 28 °C. Alternatively, grafting PNIPAAM on alginate chains, hydrogel enhances the mechanical strength of the formed hydrogel [112, 113], while the equilibrium of swelling kinetics rates reached in 3 h and declined upon rising irradiation dose and decreased considerably between 30 °C and 35 °C due to the phase separation of PNIPAAM at 32 °C.

6 Conclusion

With the current understanding that hydrogel can act as promising materials in biomedical and pharmaceutical applications, researchers are now able to develop sensitive smart hydrogels to have a response based on external changes in pH,

temperature, ionic strength, solvent composition, the presence of salt ions, light, or electric field. Many polysaccharides demonstrate several unique properties to be smart hydrophilic biopolymer as pH-sensitive hydrogels such as chitosan and alginate. Several modifications of both chitosan and alginate were reported via grafting with thermosensitive polymers such as polyacrylate derivatives to exhibit its thermosensitive character. The new dual character of these polysaccharides enables scientists to develop a series of smart hydrogels for different applications.

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Polylactic Acid-Based Hydrogels and Its Renewable Characters: Tissue Engineering Applications

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Contents

Abstract

Derived from renewable sources, polylactic acid (PLA) is a thermoplastic aliphatic polyester, which is biodegradable and bioactive and being explored for various applications. PLA being hydrophobic in nature, often needs to be used in combination with a hydrophilic moiety in order to form hydrogels. PLA based

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hydrogels have found significant attention in biomedical applications. Hydrogels resemble the structure of many tissues and can be delivered to the patient using minimally invasive surgery along with their ease of processability which makes them potential scaffold materials. PLA is often considered a suitable candidate for scaffolds due to its biocompatible and bioresorbable nature. The current chapter highlights the importance of PLA based hydrogels in biomedical applications with significant focus on scaffolds for the treatment of damaged tissues. The essential criteria for selection of suitable materials to be used in combination with PLA for tissue engineering applications is presented, which would mimic the host tissue structure and allow the natural regeneration of tissue. Several case studies involving the use of PLA based hydrogels in tissue regeneration with their significant outcomes have been discussed. Furthermore, the investigations on cytotoxicity, cell adhesion, and proliferation are outlined for identifying the scope of these materials in tissue engineering applications.

Keywords
PLA · Hydrogels · Tissue engineering · Biomedical

1 Introduction

Hydrogels are three-dimensional networks of hydrophilic polymers, which are physically or chemically crosslinked structures. Hydrogels are known to absorb excess amount of water and resemble living tissues in their swollen state. Different combination of crosslinkers or copolymers can be utilized to tailor the possible physical and mechanical properties of hydrogel structures. Hydrogels were the first biomaterials developed by Wichterle and Lim in 1960 for their clinical use as soft contact lenses using crosslinked poly(2-hydroxyethyl) methacrylate (pHEMA) [1]. Since then, hydrogels found significant acceptance in various biomedical applications such as controlled drug delivery [2], neural implants [3], artificial vitreous body [4], injectable therapeutics [5], self-healing systems for vascular repair [6], biomedical devices [7], repair of osteochondral defects [8], cartilage and bone tissue engineering [9], abdominal tissue regeneration [10], soft artificial muscles [11], etc. Additionally, they have been used for diverse applications including nanoprobes for AFM (atomic force microscopy) [12], microfluidics, soft robotics, electrical circuits and mechanical devices [13], microphones for under-water listening [14], actuators, and robots [15] which have shown their potential in electronic and electrical applications. Liang et al. used hydrogels for cleaning stains from paper artwork in order to preserve the historical cultural relics [16]. Furthermore, Wu et al. developed hydrogels using green routes for water and humidity detection [17]. Moreover, hydrogels have also been utilized for the removal of water-soluble dyes [18], controlled release of pesticides [19], and as a matrix for carbon sequestration [20], which have made them versatile and promising materials. The structure of these hydrogels has a fair control on the properties important for biomedical applications such as mechanical strength and porosity. Hydrogels can be utilized for tissue

engineering application as they are soft and rubbery in nature along with having the capability to retain an ample amount of water. Tissue engineering is aimed at reconstructing lost organs/tissues. Various tissues can be engineered by utilizing scaffolds, which serve as templates where the cells adhere and colonize to synthesize the host tissue. It is important to design scaffolds with the structure and hierarchy similar to the host tissue in order to direct the growth and formation of new tissue [21, 22]. Repair and regeneration of tissues such as cartilage, bone, muscle, nerve, tendon, etc., have been attempted by various scientific groups by utilizing 3D scaffolds. In order to accomplish the properties of scaffold, various biomaterials including synthetic and natural polymers have been explored for their use in tissue engineering applications. Natural polymers such as polynucleotides, polypeptides, and polysaccharides are known for their biocompatibility and lack of immune response but they do not have sufficient mechanical strength. Synthetic polyesters such as polylactic acid (PLA), polyglycolic acid (PGA), polyethylene glycol (PEG), polycaprolactone (PCL), etc., overcome the drawbacks of natural polymers and are synthesized by traditional polymerization mechanisms to achieve the desired properties. Among various polymers, PLA has been explored by various researchers for tissue engineering applications due to its biocompatibility, biodegradability, and mechanical strength. However, due to the hydrophobic nature of PLA, it is often used in combination with hydrophilic polymers to form hydrogels. The current chapter focuses on the hydrogels made from PLA and its copolymers to explore its potential as a scaffold for reconstruction of lost or damaged tissues.

2 Hydrogels in Tissue Engineering

Tissue engineering aims at developing artificial organs/tissues using porous, interconnected networks (scaffolds) that would mimic the structure of the host tissue. This involves seeding of cells onto the scaffolds that work as templates for providing three-dimensional structure to the regenerating tissue. For the scaffolds designed to be implanted into the human body, the cells can be seeded in vitro onto the scaffold prior to implantation or patient's own cells would infiltrate onto the scaffolds in vivo post implantation. The ideal scaffold must allow for cell adhesion, cell-biomaterial interaction, and extracellular matrix (ECM) deposition; permit the transport of nutrients, gases, and growth factors; must not elicit any inflammatory response; and degrade at a rate of the formation of new tissue. Various natural and synthetic biomaterials have been reported for their use as scaffolds in tissue engineering applications. However, it is important to select the material based on the properties of the host tissue to be regenerated. Also, it essential for a material to be biocompatible and degrade in the body without leaving any harmful degradation products. Various natural polymers including chitosan, collagen, alginate, gelatin, hyaluronic acid, etc., are known for their biocompatibility [23]. However, these natural polymers suffer from several drawbacks such as batch variability, poor control over their properties, poor mechanical strength, and difficulty in processing. Therefore, synthetic polymers are now being studied by various scientific groups for tissue

engineering applications, which are relatively easy to process and possess a good control over the material properties along with their high mechanical strength. The synthetic degradable polymers reported for their wide biomedical applications are poly(hydroxy acids) such as PLA, PGA, poly(lactic-co-glycolic acid) (PLGA), and PCL, which result in the formation of nontoxic hydroxy acids via hydrolytic cleavage of their ester bonds. These are the polymers that can be degraded into their monomers and absorbed by the metabolic pathways [24]. It is noteworthy to mention that PLA and PGA have been approved by United States Federal Food and Drug Administration (FDA) for certain clinical applications. These polymers were not designed for tissue engineering applications; however, the modifications in the degradation behavior, mechanical properties, and bioactivity have led to their extensive exploration for guiding tissue regeneration [25].

Hydrogels can be recognized as a class of polymeric materials with a water content of $\geq$90% by weight. Hydrogels are used as scaffolds as they provide biomimetic 3D microenvironment for the cell growth. They have been utilized for engineering various tissues as they resemble the natural ECM in structure and composition and can be easily designed to control cell adhesion, biological responses, biodegradability, and biocompatibility along with structural integrity. Further, it is important to use hydrogels that create high surface area to volume ratio so as to mimic the natural pore size, cell adhesion, biodegradability, biocompatibility, and mechanical strength of the host tissue to be regenerated. In order to promote a new tissue formation, the hydrogels must meet certain physical and chemical criteria such as degradation, mechanics, and cell adhesion [26]. Also, the hydrogels must be biocompatible, i.e., exist in the body without causing any damage to the adjacent cells, should not lead to the formation of scar tissue and elicit any undesirable or inflammatory response. Hydrogels can be fabricated via different techniques to be implanted directly into the body via surgery. These are the scaffolds that are designed to mimic the body tissues and work as extracellular matrix for cell adhesion and proliferation. Additionally, these hydrogels can be injectable, which are sols at room temperature and form gel at the body temperature after they have been injected. Injectable hydrogels are easy to process and require minimally invasive surgery, which increase the patient compliance. Figure 1 demonstrates implantable and injectable hydrogels for representative bone tissue engineering application.

Mechanical properties of the hydrogels are important parameters that must be considered while designing scaffolds. Tensile strength, modulus, elongation, etc., of the scaffold are related to the cell adhesion and gene expression which in turn depend on the type of crosslinking molecules, density of crosslinking, polymer chain rigidity, and swelling. Further, it is essential to design hydrogels with a controlled rate of degradation which is specific for different tissues. The degradation rate of scaffold is closely related to the mechanical properties. However, soft hydrogels are known to have degradation times longer than that of stiffer hydrogels.

Cell adhesion and differentiation are affected significantly by the interaction of cells with the hydrogels where the inappropriate interaction could lead to the formation of undesirable tissue [27]. Therefore, it is essential to consider all the

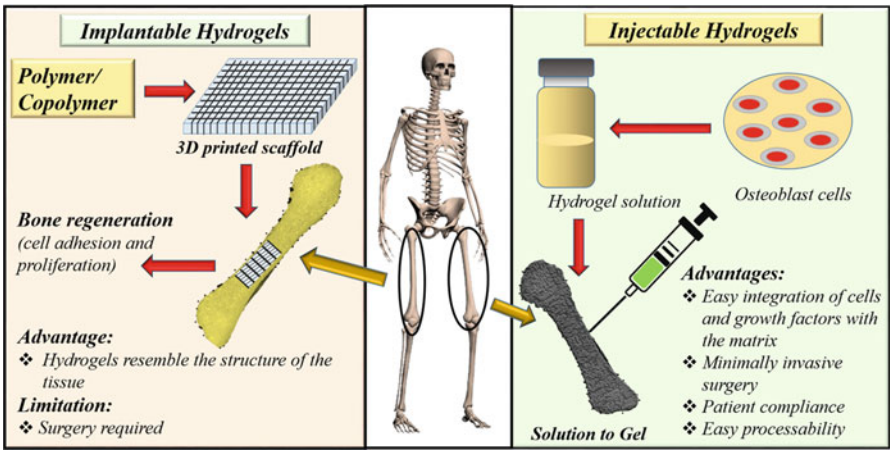

Fig. 1 Implantable and injectable hydrogels for tissue engineering application

Table 1 Moduli of native tissues present in the body

Tissues in the body	Modulus (kPa)	References
Nasal cartilage	234 ± 27	[28]
Right lobe of liver	270 ± 10	[29]
Nucleus pulposus	~10	[30]
Eye lens	~10	[30]
Bovine articular cartilage	990 ± 50	[31]
Canine kidney cortex and medulla	~10	[30]
Femur	$(18.6 \pm 1.9) \times 10^6$	[32]
Tibia	$(11.8–20.9) \times 10^6$	[33]
Humerus	17.5×10^6	[34]
Radius	18.9×10^6	[34]

parameters essential for developing hydrogels that could function as ideal scaffold materials. Table 1 displays the moduli of various tissues present in the body. The scaffolds for engineering damaged tissues must match the properties of the tissues for appropriate regeneration of the tissue.

3 Polylactic Acid (PLA)

PLA is an aliphatic polyester that belongs to the family of α-hydroxy acids. Being derived from renewable sources such as corn starch, sugarcane, cassava roots, potatoes, etc., PLA has been widely accepted as an alternative to petroleum based polymers such as polyethylene, polypropylene, polyethylene terephthalate, etc. PLA can be synthesized from lactic acid by polycondensation. Lactide is another precursor derived from lactic acid, which leads to the formation of PLA by ring opening polymerization. Reinhold

Grueter first patented the process for the synthesis of lactide in 1913 [35]. PLA is thus produced by combined fermentation and polymerization processes. The synthesized PLA can further be processed using different approaches for intended applications. Swedish Chemist Carl Wilhelm Scheele isolated lactic acid (basic constituent of PLA) from sour milk in the eighteenth century [36]. The chiral nature of lactic acid leads to the formation of two enantiomerically pure homopolymers of PLA, i.e., poly(L-lactic acid) (PLLA) and poly(D-lactic acid) (PDLA) acid [37]. The two enantiomers are found to have different rates of degradation. PLLA is known for its prolonged biodegradation and superior biocompatibility as compared to that of PDLA. Further, the strength and modulus of PDLA are relatively low as compared to PLLA. These polymers are found to have a crystalline nature [38]. Racemic mixture of D-lactic acid and L-lactic acid on polymerization forms poly(DL-lactic acid) (PDLLA) that is amorphous in nature. PLA can be produced using several polymerization techniques such as ring opening polymerization, solid-state polymerization, condensation polymerization, and azeotropic dehydrative condensation. The properties of PLA vary with the molecular weight, and therefore it is essential to consider the molecular weight for intended applications. PLA can be synthesized via polycondensation or ring opening polymerization. However, ring opening polymerization takes relatively less time for the production of PLA. Wallace H. Carothers reported the ring opening polymerization of lactide in 1932 [39]. PLA was considered to be an undesirable material due to its instability in the humid conditions. However, PLA started gaining importance in biomedical field in 1966 due to its biodegradable, bioresorbable, biocompatible, and nontoxic nature. The synthesis of PLA usually involves the use of tin octoate ($Sn(Oct)_2$) as a catalyst which is less toxic to human body and has been approved by Food and Drug Administration (FDA) for pharmaceutical and biomedical applications [40]. The recent approaches involve the use of lipase for the synthesis of PLA, which will eliminate the use of metal based catalysts. Such greener approaches are still at the stage of development. The degradation products of PLA are usually water and carbon dioxide which are nontoxic and noncarcinogenic to the body. PLA has therefore gained significant attention due to its excellent biodegradability and biocompatibility. It has been studied for its application in the biomedical field such as drug delivery, orthopedic fixation devices, surgical sutures, dental implants, and scaffolds for engineering damaged tissues.

PLA is a versatile polymer that is known to have high mechanical strength and modulus and has been explored in various applications including food packaging, agriculture, electronics, textile, paper coating, etc., due to its unique properties. The conventional petroleum based polymers take several hundred years to degrade completely, whereas PLA, after its service life, can go back to nature in the form of water and carbon dioxide and degrade completely over several months to few years. However, it has low impact toughness and a small window for processing, which may be improved by blending, stereocomplexation, or co-polymerization. A small amount of PDLA is generally added to PLLA in order to improve the processability; however, it decreases the crystallinity of the polymer. Blending of PLA with suitable polymers enables to achieve increased crystallinity, improved toughness, and elongation at break along with tailored hydrolytic degradation [41]. PLA, although having significant potential for replacing conventional plastics, is not

Table 2 Properties and degradation rates of polymers/copolymers

Sr. No.	Polymer	T_m (°C)	T_g (°C)	Tensile strength (MPa)	Modulus (MPa)	Time of degradation (months)	References
1.	PLLA	~175	~62	~41	~1196	24–60	[25, 49–51]
2.	PDLA	~177	~61	~46	–	24–60	[25, 50, 52, 53]
3.	scPLA	~206–230	65–72	~880	~8600	–	[25, 45, 49]
4.	PGA	225–230	35–40	~384	~12.8	6–12	[25, 54–56]
5.	PLGA	–	45–55	~4.3	1000–2000	1–6	[25, 57]
6.	PCL	60	−60	10–16	400	>24	[25, 58]

PLLA poly(L-lactic acid), *PDLA* poly(D-lactic acid), *scPLA* stereocomplex PLA, *PGA* polyglycolic acid, *PLGA* poly(lactic-co-glycolic acid), *PCLA* poly(caprolactone-co-lactic acid)

currently used on a large scale as the cost of manufacturing PLA is higher as compared to that of petroleum based polymers due to the complicated steps of synthesis. Additionally, the low heat deflection temperature, relatively low glass transition temperature, low melting temperature, relatively poor barrier properties, and slow crystallization have limited its use in many applications. Various scientific groups have attempted to enhance these properties of PLA by utilizing methods such as formation of biocomposites [42, 43], copolymerization, blending of polymers [41, 44], formation of stereocomplexes [45, 46], etc. Addition of biofillers such as chitosan, clay, cellulose, hydroxyapatite, bioglass, etc., into the PLA matrix leads to the formation of biocomposite with improved properties. Further, the incorporation of bioactive fillers such as bioglass will allow for the regeneration of bone tissue, which has gained significant attention in the recent past [47]. Thermal, mechanical, as well as thermomechanical properties of PLA can be enhanced by blending with suitable polymers. Stereocomplexation involves mixing of enantiomers in 1:1 ratio, which is found to increase the melting temperature by 50 °C as compared to that of pure enantiomeric PLA. Thermal, mechanical, and gas barrier properties can significantly be improved by stereocomplexation, which is a crystal formed by the interaction between enantiomers of PLA. Further, PLA is known to be hydrophobic in nature along with slower rate of degradation, which is undesirable for many biomedical applications. However, copolymerization with hydrophilic monomers or the incorporation of polyethylene glycol (PEG) chains in the backbone of PLA can lead to the formation of water soluble PLA based polymers, which can be explored for the formation of hydrogels for engineering diseased or damaged tissues [48]. Stereocomplexation of copolymers can further enhance the mechanical, physical, and chemical properties of the hydrogels, which can be tailored for desired specific applications. The following sections will discuss in detail about hydrogels containing polylactic acid and its copolymers. The properties and degradation rates of polyesters have been displayed in Table 2. The rate of degradation of the polymer can be tailored by using different combination of polymers for desired tissue regeneration.

4 PLA Based Hydrogels

The hydrophobic nature of PLA along with its hydrolytic stability has hindered its use in many biomedical applications utilizing hydrogel networks. However, it is possible to alter the physical properties of PLA by copolymerization with a wide range of hydrophilic polymers such as polyethylene glycol (PEG), polyurethane (PU), polyethylene oxide (PEO), etc. Copolymerization is a promising strategy to tailor the amphiphilic behavior of PLA along with its physical and mechanical properties. Polymers such as PEG, PEO, polyurethanes, and polysaccharides when used with PLA lead to some special properties that are explored for various biomedical applications. Further, it is possible to obtain stimuli-responsive hydrogels by adjusting the ratio of individual polymers forming the copolymer. Additionally, stereocomplexation between the copolymers have widened the application of PLA in biomedical field. It is known that the optically pure stereoisomers, which are isotactic, would ease the formation of stereocomplex PLA [59]. PLA based hydrogels developed by copolymerization and stereocomplexation are thus gaining acceptance in the field of tissue engineering where the properties of the hydrogel can be tailored to meet the intended applications. Various case studies based on PLA based hydrogels and their applications in biomedical field, specifically tissue engineering applications, have been discussed in the following subsections.

4.1 Polylactic Acid (PLA): Polyethylene Glycol (PEG) Based Hydrogels

PLA based hydrogels are often made by using PEG in combination as it is hydrophilic in nature. Although nonionic in nature, PEG is water soluble and elicits thermo-responsiveness along with being biocompatible in nature. Therefore, it has been widely studied for its use as hydrogel for tissue engineering application. PLA-PEG copolymer, due to its thermo-responsive nature, is water-soluble at room temperature and forms into gel at body temperature, i.e., ~37 °C. Further, crosslinked hydrogels can also be synthesized by stereocomplexation. Two segmental arrangements of triblock copolymers with PLA and PEG are possible, viz., PLA-PEG-PLA and PEG-PLA-PEG. The stereocomplexation of enantiomers in these block copolymers manifests unique material properties. The triblock copolymers are predominantly produced by ring opening polymerization of lactide onto the PEG-diol in presence of stannous octoate as a catalyst [59]. Triblock polymers PLLA-PEG-PLLA and PDLA-PEG-PDLA lead to the formation of gel at body temperature. Varying the molecular weight of lactide can lead to the improvement in the mechanical properties of these hydrogels. Further, thermo-responsive hydrogels based on diblock PEG-PLLA and PEG-PDLA have also been explored. The gelation of diblock copolymers is faster along with higher gel storage modulus as compared to triblock copolymers. The block length of PEG significantly alters the gelation. For a triblock copolymer, PLA of the triblock enters into the micelle and forms a stereocomplexed solution if the PEG blocks are smaller than the distance

between micellar cores. Loosely crosslinked gels are formed if the block length of PEG is too large. Stereocomplex based hydrogels are ideal for injectable tissue engineering scaffolds pertaining to their high mechanical strength. Further, the hydrogels made from star PEG and PLA block copolymers possess different properties and gelation behavior as compared to linear block copolymers, which have been explored by various researchers. PLA-PEG based hydrogels are thus considered to be the potential candidates for hydrogel synthesis due to their biodegradability along with controlled release properties. Such hydrogels can be tailored to obtain controlled drug release over a period of month. In case of short chain PEG, the block copolymers are difficult to be solubilized in water, which further restricts the use of high molecular weight PLA for the fabrication of hydrogels. To overcome this drawback, poly(D,L-lactic acid-co-glycolic acid) (PLGA) is often used in combination with PEG [60]. It has been reported that cell adhesion, proliferation, and differentiation can be adjusted by electrical stimuli. Upon application of the external stimuli, a considerable change in surface charges is observed along with the surface properties such as conformation and wettability that influence the cell behavior. With the aim of developing biomimetic functional scaffolds, Cui et al. designed injectable electroactive hydrogels by coupling tetra aniline with enantiomeric PLA-PEG-PLA [61]. The electroactive nature of the hydrogels was confirmed by UV-Vis spectroscopy and cyclic voltammetry. The stereocomplexation between the blocks of PLLA and PDLA induced the gelation which was affected by the temperature, time, as well as PLA block length. The rigidity of tetra aniline blocks along with copolymer interaction imparted more regular structure to the hydrogels. The biocompatibility studies demonstrated that the electroactive hydrogels were suitable for applications in vivo. On application of pulsed electrical simulation, the hydrogels were observed to enhance the proliferation of fibroblasts, preosteoblasts, and cardiomyocytes, which exhibit their promising applications in tissue engineering. Amphiphilic block copolymers provide a sol to gel transition with change in temperature, which is influenced by the molecular weight and the copolymer structure. Such hydrogels can be used as injectable materials when their sol to gel transition is close to body temperature. This will eliminate the need for the surgery required to insert the implants in the body wherein the incorporation of cells and proteins will be easy. In this line, Buwalda and his group developed acrylate functionalized 8-armed star block copolymers of PLA and PEG by physical crosslinking and photo-polymerization. The stereocomplexation of block copolymers resulted in in-situ gelation. Further, photo-polymerization led to the improvement in the mechanical properties along with the stability of hydrogels. The amide linkages between the blocks of PEG and PLA and the high crosslink density resulted in resistance against hydrolytic degradation. These injectable star block copolymers were found to have promising applications in controlled drug delivery. Ring opening polymerization (ROP) of L-lactide was carried out using trimethylolpropane as an initiator and stannous octoate as a catalyst to synthesize three-armed polylactic acid where the molar ratio of initiator and monomer was varied to tailor the arm length [62]. Polyurethane was synthesized from linear polyethylene glycol and three-armed polylactic acid, which formed hydrogels upon mixing with water. The water retention of the

hydrogels was found to be 38 times that of polyurethane prepolymer, which also had good mechanical properties. The developed poly(urethane-urea) hydrogel was low cost, biodegradable in nature with high content of water.

4.2 Poly(Lactic-Co-Glycolic Acid) (PLGA): Polyethylene Glycol (PEG) Based Hydrogels

Poly(lactic-co-glycolic acid) (PLGA) is a copolymer of PLA and PGA, which are the polymers often used in combination to tailor the degradation rate of scaffold. Various forms of PLGA are obtained depending on the lactide to glycolide ratio. This copolymer is found to be less crystalline which degrades relatively faster as compared to the individual homopolymers. PLGA is widely being explored as a scaffold material as it is biocompatible and it is possible to tailor its rate of degradation. PLGA is soluble in various solvents such as tetrahydrofuran, acetone, ethyl acetate, and chlorinated solvents unlike PLA and PGA which are poorly soluble. These copolymers at room temperature exist in liquid form, which are formed into hydrogels instantaneously at body temperature. PLGA-PEG hydrogels possess superior mechanical properties as compared to that of PLA-PEG based hydrogels. Further, these copolymers are hemo-compatible and suitable for various applications. The physico-chemical properties of the end product are significantly affected by the process parameters and synthesis mechanisms of PLGA. The gelation mechanism of these block copolymers vary with the PLGA blocks placed at the end or middle. For instance, PLGA-PEG-PLGA lead to the formation of micelles and inter-micellar bridges forming a gel at lower temperature. Whereas PEG-PLGA-PEG leads to the formation of hydrophilic shell with a lipophilic core. Various factors such as block ratio, molecular weight of polymers, end group, and concentration are essential in controlling the gelation and degradation behavior of these block copolymers. Further, the rate of degradation of PLGA is highly influenced by its sequence. Random PLA prepared by ring opening polymerization degrades faster than analog-sequenced PLGA [63]. It is possible to tune PLGA-PEG based system to form gel specifically at 37 °C, which makes them ideal for delivery vehicles and depots. However, enhanced mechanical strength and extended biodegradability is essential for tissue engineering applications. The degradation products of polyesters being acidic in nature are harmful to the cells and tissues. To overcome this limitation, bioactive ceramics such as hydroxyapatite are used in combination with polyesters. Hydroxyapatite is known for its biocompatibility, biodegradability, and osteoconductivity. Incorporation of hydroxyapatite to the polyesters enhances the mechanical properties of the material along with imparting bioactivity. In this line, PLGA-g-PEG based injectable hydrogels containing hydroxyapatite were developed by Lin et al. for bone tissue engineering application [64]. The grafted polymer was synthesized by ring opening polymerization using stannous octoate as a catalyst. Hydroxyapatite in varying ratios was added to PLGA-g-PEG hydrogel which resulted in the formation of hydrogel

composites. Thermo-sensitive hydrogel composites resulted in gel formation at body temperature with an enhancement in the storage modulus. Further, the acidic release off the grafted polymer was neutralized by the incorporation of hydroxyapatite. The resulting composites were found to be suitable for the release of amphiphilic drugs for bone regeneration.

4.3 Poly(ϵ-Caprolactone-Co-Lactic Acid) (PCLA): Polyethylene Glycol (PEG) Based Hydrogels

Caprolactone is often copolymerized with lactide in order to overcome the shortcomings of PLA or PLGA copolymers. Due to its longer chains, caprolactone provides a larger window for gel formation along with slow degradation. PLA and PLGA system tend to degrade faster resulting in the accumulation of lactic and glycolic acid, which may lead to the rapid degradation of hydrogels. However, PCLA is found to degrade slowly which leads to a lower accumulation of acids. Biodegradable triblock copolymer (PCLA-PEG-PCLA) was synthesized by Zhang et al. by ring opening polymerization [65]. The aqueous solution of the polymer resulted in the formation of injectable hydrogel due to the formation of self-assembled network of micelle at the body temperature. The hydrogel was tested in vivo in rabbits as a barrier for preventing the postoperative intestinal adhesion. The in vitro and in vivo studies demonstrated that the hydrogels were biodegradable and their integrity could be retained up to several weeks. The hydrogel was found to be convenient and effective in reducing the formation of postoperative tissue adhesion. Polyester and polyether based thermo-reversible hydrogels are gaining significant importance due to their biodegradability and persistence. However, in order to eliminate the need for the surgery for tissue regeneration, the concept of injectable hydrogels was evolved. These are liquid at room temperature which undergo gelation in the body. Scaffolds made of injectable hydrogels are capable of filling the bone defects of any shape. Further, it is easy to incorporate the growth factors in the liquid form without the requirement of solvents. The material used for injectable hydrogels must be biocompatible with sufficient mechanical stability along with tailored rate of biodegradation. To explore the potential of such hydrogels in bone tissue engineering, Kim et al. synthesized dual stimuli responsive block copolymer based on PLGA-PEG and sulfamethazine oligomer (SMO) wherein SMO was grafted chemically to the thermo-responsive PCLA-PEG-PCLA block copolymer [66]. This block copolymer was found to form gel at pH 7.4 and resulted in formation of sol at pH 8. In vitro studies were conducted which resulted in the highly biocompatible nature of the hydrogels. Human mesenchymal stem cells were encapsulated by the polymer solution, which was injected in the mice for ectopic bone formation. The cells showed the differentiation up to 7 weeks and the results indicated the bone mineralization along with high alkaline phosphatase activity. The developed copolymer thus displayed promising applications as injectable scaffold for bone tissue engineering.

4.4 Polylactic Acid (PLA): Polyethylene Oxide (PEO) Based Hydrogels

Polyethylene oxide (PEO) is a synthetic biomaterial which is used in combination with PLA to combine the biodegradability of PLA and hydrophilicity of PEO. It is known that the amphiphilic nature of PLA-PEO based triblock polymers leads to the formation of hydrogels. These amphiphilic block copolymers tend to form physically crosslinked networks where it is not necessary to use the crosslinking agent. However, chemical crosslinking may lead to the enhancement in cell adhesion to the scaffold along with more permanent 3D structure. When physically crosslinked PLA-PEO-PLA hydrogels are exposed to aqueous media, they swell and finally dissolve in solution ultimately leading to the loss of its mechanical integrity, which can be overcome by using chemical crosslinking. With the aim of controlling the network structure of hydrogels, Sanbaria-DeLong and his group used acrylates to modify the end groups of PLA-PEO-PLA triblock copolymer where the physical structures were converted to chemically crosslinked hydrogels by photo crosslinking [67]. They obtained better results for the photo-crosslinked gels as they remained intact in aqueous environment. Further, the photo crosslinked gels showed a decrease in modulus which can be tailored by controlling the concentration of polymer for specific tissue engineering applications. The effect of molecular composition and polymer structure on the gel strength was studied by Bhatia and Tew [68]. The stiffness of the block copolymer was varied by changing the length of PLA end blocks along with altering the physical crosslinking. This was done by functionalizing the end groups of the copolymer with acrylates, which provided more insights toward the association between molecular structure and bulk properties. Rheological properties of hydrogels based on PLLA-PEO-PLLA triblock copolymer were studied by Aamer et al. [69]. ROP of L-lactide in presence of stannous octoate was carried out in order to fabricate the triblock copolymers containing large PEO and varying blocks of PLLA. It was found that the block length of PLLA significantly affected the elastic modulus of hydrogels, which can be the controlling parameter for soft tissue engineering applications. The elastic moduli of gels were found to mimic the soft tissues, which make these triblock copolymers as promising candidates for soft tissue engineering applications.

4.5 Polylactic Acid (PLA): Polymethacrylate Based Hydrogels

Amphiphilic block copolymers of PLA/polymethacrylate are generally synthesized by controlled free-radical polymerization. Incorporation of methacrylates into the copolymer system leads to the tailored properties to meet the targeted applications. Variation in the functional substitute groups could easily tune the hydrophilicity of the polymer along with stimuli induced phase behavior. Poly (N-isopropylacrylamide) (PNIPAAm) is found to have a lower critical solution temperature of 32 °C, which is similar to that of human body. It is a well-known

Table 3 Properties of different polymer based hydrogel systems

Sr. No.	Polymer hydrogel system	Modulus (kPa)	Tensile strength (kPa)	Toughness ($kJ.m^{-3}$)	Water retaining capacity by mass (%)	Swelling ratio	References
1.	PLA/alginate	189.8 ± 62.8	–	–	–	–	[72]
2.	Poly(urethane-urea)	–	~108	–	91%	–	[62]
3.	Poly (N-isopropylacrylamide)/ chitosan	–	–	–	1500%	–	[70]
4.	PEG/OTMC (oligo tri-methylene carbonate)	14.9 ± 0.2	–	215.3 ± 46.4	43%	–	[73]
5.	Poly (N-isopropylacrylamide)/ starch	8.44 ± 0.13	–	–	–	17.2 ± 0.6	[74]
6.	Chitosan/dextran-polylactide/ glycerophosphate	~13 kPa	–	–	–	–	[75]
7.	PLA/organoclay nanocomposite	–	~64.4	–	–	–	[76]

thermo-responsive polymer that can be used for specific biomedical applications. PNIPAAm-PLA-PNIPAAm triblock copolymers are found to have great potential in targeted drug delivery [9]. PNIPAAm was synthesized by precipitation polymerization by Temtem et al. in supercritical carbon dioxide which avoids the need of drying before processing or characterization unlike conventional polymerization methods [70]. Since carbon dioxide is nonflammable, nontoxic, and highly pure, it was used as a polymerization medium. Supercritical carbon dioxide was used as a green solvent for the preparation of smart hydrogels for tissue engineering applications by combining the biocompatibility of chitosan and thermos-responsiveness of PNIPAAm. The hydrogels with the thermo-responsive nature can be used as scaffolds for tissue engineering application. Polymethyacrylates can be tailored to provide good cellular adhesion by utilizing suitable polymers in combination. Amphiphilic copolymers are known to be excellent substrates for cells. Johnson et al. modified polymethacrylate based hydrogels using photo-polymerization functionalized with fibrinogen [71]. Different mechanisms were observed to be utilized by the cells to attach and grow in various systems. Further, the effect of the alkyl group strongly influenced the cell adhesion. Transglutaminase was shown to catalyze the attachment of fibrins to the hydrogel. Polymethacrylates are thus finding applications in biomedical applications by tailoring their properties and function. Further, the chemical and physical properties of the material can be tuned by functionalizing with suitable materials.

The above studies demonstrate the potential of polylactic acid in tissue engineering applications. PLA is thus gaining significant acceptance for biomedical applications due to its versatile nature. Tailoring the properties of PLA by using different polymers renders it a suitable candidate for designing hydrogels. Table 3 highlights the properties of different hydrogel systems based on polymers, which are promising candidates for various tissue engineering applications.

5 Design Criteria for Scaffolds

Scaffolds for tissue engineering application must fulfill certain design criteria in order to allow ideal tissue formation. Tissues to be engineered involve the use of biomaterials, cells, and cell-matrix interaction. It is important to consider various parameters while selecting cells and scaffold materials for the targeted tissue such as type of cells, cell adhesion to the biomaterial, mechanical properties, porosity, structure, and hierarchy of the scaffold. These parameters vary for different tissues in the human body, and therefore care must be taken for designing the scaffolds according to the design criteria for the targeted tissue.

The material used for designing scaffold along with the hierarchy play a vital role in the formation of an ideal tissue by providing temporary mechanical function, preserving the volume of tissue, and delivering the bio-factors such as cells, genes, or proteins. In other words, the material for the synthesis of scaffold must be selected based on the physical properties, mass transport properties, and biological interaction required for specific applications. The scaffolds must be nontoxic to the cells including the surrounding tissue and must allow the nutrient diffusion along with mechanical strength to withstand the load in vivo. Mechanical function and cell delivery must be balanced by the scaffold such that the regenerating tissue assumes the properties and function while the scaffold degrades. Design characteristics of the scaffold significantly affect its mechanical and biological performance which are essential in engineering the tissue with required function and properties. Scaffolds for tissue engineering must be designed with the hierarchy and porosity in order to achieve the required mass transport and other mechanical properties.

Further, the methods used for the fabrication of hydrogels for tissue engineering must be selected based on the gelation of hydrogels.

5.1 Mechanical Properties

The functional properties of the scaffold along with the cell-matrix interaction are dependent on the material chemistry and processing conditions. Various mechanical properties including modulus, compression, tensile strength, elongation at break, etc., are the most important parameters to be considered while designing scaffolds for regeneration of tissues. Further, the hierarchy of the scaffold must exactly mimic the tissue to be regenerated in order to allow for ideal tissue regeneration. The scaffolds must be designed so as to withstand the temporary load in vivo and must provide the environment to the cells for their activity. The scaffold must provide temporary support to the cells where they could enter, grow, and organize themselves in order to synthesize their own extracellular matrix. When designing scaffolds for bone tissue engineering, an important aspect to be considered is the bone mineralization. The modulus of elasticity increases with the mineral content of the bone. However, it significantly lowers the shock absorption capacity of the bone. The ultimate strain of cortical bone is $\sim$1.25%, which is reduced to 0.4% when the sufficient water is not maintained. The environmental factors are

thus critical in bone tissue engineering. The properties such as tensile strength, modulus, compressibility, viscoelastic behavior, etc., can be controlled in order to design scaffolds for targeted tissues [22]. The density of crosslinking in hydrogels affect the mechanical properties of the scaffold, which are influenced by various parameters such as temperature, pH, crosslinker, polymer chain rigidity, swelling of gels along with the degree of porosity. The porosity of scaffold decreases with the increase in stiffness [23].

5.2 Porosity

Porous structure of the scaffold is desired for the cell nutrition, cell migration, and cell adhesion. Computer aided design (CAD) may be used to create the complex three-dimensional scaffolds with the hierarchical design. Various processing techniques have been reported for fabricating scaffolds such as stereo-lithography, laser sintering, 3D printing, wax printing, bio-plotter, fused deposition modeling, etc., which may be combined with traditional processing techniques such as gas foaming, porogen leaching to attain the desired function [77]. For a scaffold to function appropriately, it is important to have the required nutrient, gas, and cell transport to and out of the scaffold as well as within the scaffold. The molecular weight and the size of diffusion species affect the rate of diffusion [22]. The porosity of the scaffold will affect the cell migration since the cells enter the scaffolds, bind to the surface, adhere, and proliferate thereby generating the host tissue. Too small pore size may not allow cells to incorporate into the scaffold and therefore no tissue will be formed. However, too large pore size may lead to the undesired number of cells entering the scaffold, which may cause the anchorage dependent cell death. Therefore, pore size of the scaffold must be selected based to the required tissue to be regenerated.

5.3 Cell-Matrix Interaction

Interaction of tissue cells and the scaffold matrix is an important aspect in regeneration of the diseased/damaged tissue. Cell proliferation, differentiation, and cellular activities are directed by cell adhesion, which in turn is dependent on the cell-biomaterial interaction. Cell surface integrins bind with the proteins present on the surface of ECM due to which the cells adhere on the scaffold. The interactions of cells with the ECM provide anchorage and signals triggering the cell function and expression, which guides the development, organization, and maintenance of the tissue [78]. Polymers lacking the cell adhesion regions may be modified by immobilization of proteins [24]. The material used for the scaffold must not elicit any inflammatory response. Covalently coupling the ECM proteins to the polymer through cell surface receptors can lead to the formation of highly specific adhesive surface. It is possible to modify the hydrogels by certain growth factors in order to regulate the cell function [22].

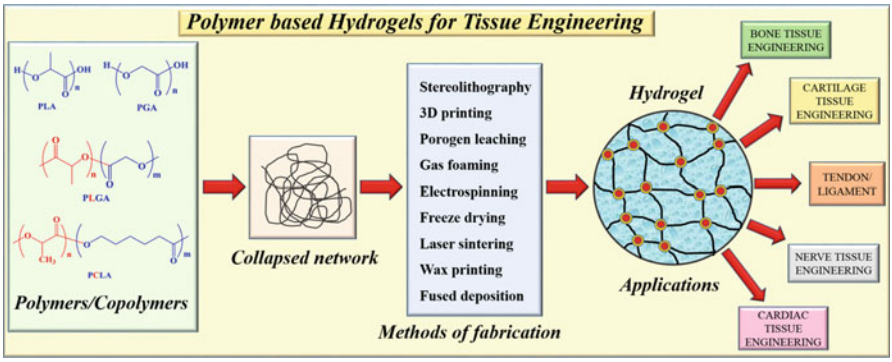

Fig. 2 Polymer based hydrogels along with methods of fabrication for tissue engineering applications

5.4 Fabrication Techniques

Several methods such as 3D printing [79], electro-spinning, electro-spraying [80], freeze drying and fixation, porogen leaching [81], and stereo-lithography [82] have been used for the development and designing of the hydrogel and scaffolds of polymer system. Figure 2 is the schematic representation of various polymer based hydrogels for tissue engineering applications along with various methods of fabrication. It is vital to take into account the properties of the scaffold desired for targeted applications, which can be tuned during their fabrication.

Several materials including PLA [83], PLGA [63, 84], chitosan, alginate [85], etc., along with their fabrication techniques [86] and applications are listed in Table 4. The extensive use of PLA based hydrogels demonstrates its possible future scope for the treatment of damaged tissues or organs, which can gain widespread acceptance for targeted applications.

5.5 Degradation Rate of Scaffolds

The scaffold for the tissue engineering application must have a controlled rate of degradation. The scaffold must degrade at a rate so as to match the rate of formation of the new tissue, which can be tailored by blending or copolymerization [24]. The rate of degradation is also important in controlled release of bioactive molecules. It is therefore essential to understand the rate as well as the mechanism of degradation. The basic degradation mechanisms of hydrogels include hydrolysis, dissolution, and enzymatic degradation. Hydrolysis of the ester linkages present in PLA leads to its degradation. The rate of degradation of PLA based copolymer gels can be tailored by changing the block length. However, the surrounding environment does not affect the rate of degradation of hydrogels. Many biopolymers including chitosan and collagen are found to degrade by the enzymatic action. The availability

Table 4 Methods of preparation of scaffolds and their applications in tissue engineering

Sr. No.	Polymer system	Method of preparation	Application	References
1.	PLA	Electrospinning	Porous structures For membrane and tissue engineering applications	[87]
2.	PLA	Electrospinning	Neural tissue engineering	[88]
3.	PLCL/Poloxamer Nanofibers	Electrospinning	Skin tissue engineering	[89]
4.	PLA	Electrospinning	Cartilage tissue regeneration	[90]
5.	PLLA	Freeze-fixation and freeze-gelation	Tissue engineering	[91]
6.	PLGA			
7.	Chitosan			
8.	Alginate			
9.	Ca-alginate/chitosan	Electro-spraying	Encapsulation of bioactive compounds and organisms	[92]
10.	Poly(D,L-lactide-co-glycolide)	Compression molding method	Tissue regeneration	[93]
11.	Poly(D,L-lactide-co-glycolide)	Room-temperature compression molding and particulate leaching approach	Tissue engineering and tissue reconstruction	[94]
12.	Poly(D,L-lactide-co-glycolide)	Injection molding approach combined with particulate leaching	Porous foams in tissue engineering	[95]
13.	Poly(lactide-co-glycolide) and hydroxyapatite surface-grafted with l-lactic acid	Melt-molding particulate leaching method	Orthopedics and tissue engineering	[96]
14.	Poly-4-hydroxybutyrate (P4HB) and a polyhydroxyoctanoate (PHOH)	Stereolithography	Tissue engineered heart valves	[97]
15.	Gelatin	Gas-in-liquid foam templating	Tissue engineering	[98]

PLA polylactic acid, *PLCL* Poly(ε-caprolactone-co-lactide)

of enzymes in the scaffold along with the cleavage sites in the polymer will affect the rate of enzymatic degradation. Various ionically crosslinked polymers including alginate normally degrade by dissolution mechanism. Ionic environment of the scaffold will affect the rate of degradation of ionically crosslinked polymers [22].

6 Conclusion

The current chapter focuses on PLA based hydrogels for tissue engineering applications. An extensive review of various PLA based systems with their unique properties is represented. The hydrophobicity of PLA restricts its use in the hydrogel application of hydrogel, which is reported to overcome by using it in combination with polymers in order to form hydrogels. As hydrogels resemble the structure of many tissues and can be delivered to the patient using minimally invasive surgery, they are considered as ideal candidates for tissue engineering applications. Further, the design criteria for selecting materials to be used in combination with PLA for tissue engineering applications are presented. Several case studies involving the use of PLA based hydrogels in tissue regeneration with their significant outcomes have been discussed. The mechanical and physico-chemical properties of PLA could significantly be altered in order to match the host tissue to be regenerated. The properties of various polymers/copolymers for tissue engineering applications have been presented in order to select a suitable combination of system. Additionally, the fabrication techniques of hydrogels for various tissue engineering applications have been highlighted with their outcomes. PLA based block copolymers with tailored rate of degradation have been demonstrated for specific tissues in the body. The versatile characteristics of PLA thus makes it a promising candidate for tissue engineering applications.

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Protein-Based Hydrogels

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Abstract

Hydrogels have the capability to absorb large amounts of water or biological fluids into their three-dimensional hydrophilic polymer networks. These attractive materials are used to develop food additives, superabsorbents, wound dressing compounds, pharmaceuticals, and biomedical implants and also applied in tissue engineering, regenerative medicines, and controlled-release process. Hydrogels can be obtained from synthetic and/or natural resources. Synthetic hydrogels exhibit high water absorption capacities and proper mechanical strength, although their applications are being limited because of low biocompatibility and biodegradability as well as the toxicity arisen from unreacted monomers remained in the gel structure. Natural hydrogels are often derived from polysaccharides and proteins. Protein-based hydrogels have substantial advantages such as biocompatibility, biodegradability, tunable mechanical properties, molecular binding abilities, and intelligent responses to external stimuli such as pH, ionic strength, and temperature. Therefore, this kind of hydrogels is known as smart biomaterials for controlled release, tissue engineering, regenerative medicine, and other applications. Protein can be converted to hydrogel using physical, chemical, or enzymatic treatments. To improve their mechanical properties, hybrid hydrogels are synthesized by combining natural polymers with synthetic ones. The main approach to obtain hybrid hydrogels is grafting natural polymers with synthetic one and vice versa. This chapter intends to look over protein-based hydrogels. After brief introduction of protein and its structure, the properties of proteins and peptides used to develop hydrogels, as well as their preparation methods are discussed. The potential applications of these polypeptide-based hydrogels in the fields of superabsorbent development, tissue engineering, and controlled release are reported. Characterization methods for protein-based hydrogels are covered in the final section to determine rheological properties, morphology, and thermal stability.

Keywords

Hydrogels · Protein and peptide · Superabsorbent · Controlled release · Tissue engineering · Characterization · Rheological behavior

1 Introduction

Hydrogel-based technologies have been flourished in numerous fields upon the introduction of hydrogels in 1954. Inherent 3D structure of hydrogels absorbing large amount of water is composed of hydrophilic polymers. The main features of hydrogels are their insolubility and stability in aqueous solutions due to the presence of cross-linked polymer chains. Moreover, their water holding capacity varies from 1 to 1000 g/g absorbent. The mechanical properties of hydrogels can be tailor-made using chemical and physical cross-linking. Based on the cross-link nature, hydrogels are categorized as physical or chemical ones. Physical hydrogels are reversible and

stabilized by ionic and hydrogen bonds as well as hydrophobic forces. Changes in environmental conditions including pH and temperature, and addition of solutes may disrupt such hydrogels. In contrast, chemical cross-linking methods arrange covalent bonds in the body of hydrogels and make them more stable [1–8].

The first generation of hydrogels was mainly based on hydroxyalkyl methacrylate and its derivatives creating swelling capacities up to 40–50%. This kind of hydrogels was used to develop contact lenses. Nowadays, hydrogels have a wide range of applications. These attractive materials have many applications in food additives, superabsorbents, wound dressing, pharmaceuticals, biomedical implants, tissue engineering, regenerative medicines, diagnostics, controlled drug delivery, wastewater treatment, and biosensor. In addition to agricultural usage, superabsorbency of hydrogels makes them applicable for developing personal care and hygienic products such as disposable diapers, sanitary napkins, towels, sponges, and surgical pads. Hydrogels can be affected by the changes in pH, temperature, the concentration of metabolite, and osmotic pressure. In addition, specific molecules such as glucose or antigens can stimulate hydrogels. Such hydrogels can be used in biosensors and controlled-release delivery systems for drugs and chemicals [5, 9–14].

Synthetic polymers such as poly(acrylamide), polyacrylate, poly(hydroxyalkyl methacrylates), and poly(methacrylamide) and its derivatives, poly(N-vinyl-2-pyrolidone) and poly(vinyl alcohol), are currently exploited to prepare hydrogels. Although this kind of hydrogels exhibits high water absorption capacities and excellent mechanical strength, their applications are being limited because of the toxicity arisen from unreacted monomers presented in the gel structure. Moreover, low biodegradability and biocompatibility of the synthetic hydrogels may cause environmental problems [15, 16]. To overcome these challenges, natural-driven hydrogels can be proper alternatives.

In contrast to synthetic ones, natural hydrogels are biodegradable and compatible with living cell activity and often remain safe byproducts. However, natural hydrogels have inherent disadvantages such as poor mechanical strength and immune inflammatory responses. Additionally, the natural hydrogel compositions vary batch to batch; and biomaterials with animal origin, especially proteins, may transfer viruses or other pathogens to the site of application, which is so crucial in biomedical engineering applications. Polysaccharides-based and proteins-based hydrogels are the most popular examples of the natural hydrogels [17].

Proteins have inherent advantages over polysaccharides for hydrogel developments. Proteins contain several functional groups including amino, carboxyl, hydroxyl, sulfhydryl, and phenolic groups, which can act as reactive sites for chemical modifications and cross-linking. Proteins are nontoxic, biocompatible, and biodegradable. Proteins and peptides are often incorporated into hydrogels to design biomimetic materials for tissue engineering and drug delivery, since polypeptides are natural constituent of the extracellular matrix. However, some sorts of proteinous hydrogels, e.g., thermally induced ones, cannot re-swell to their original volume after drying due to the increment of protein–protein interactions via hydrogen bonding and electrostatic and hydrophobic interactions occurring as a result of dehydration. Therefore, it is crucial to enhance the swelling and water-absorbing

properties of proteinous gels, which can be obtained by appropriate chemical modifications of the constituents [6, 9, 15]. This chapter aims to review protein-based hydrogels, which is initiated by brief description of protein and its structure. Afterward, the properties of proteins and peptides as hydrogel constituents, and the corresponding hydrogel preparation methods are considered. Superabsorbent developed by protein-based hydrogels as well as their applications in tissue engineering and controlled release are reported. Rheological properties, morphology, and thermal stability of proteinous hydrogels are highlighted in the final section.

2 Protein Structure and Properties

To form a peptide bond, two amino acid molecules covalently link together through the condensation reaction between an amino group of one molecule with an carboxyl group of another one. The reaction results in the elimination of a water molecule and the formation of a dipeptide. A short sequence of amino acids is called peptide while protein, also known as polypeptide, refers to longer chains of amino acids. Amino acids in the structure of peptides or proteins are called residues to be distinguished with the free form. Proteins may contain 20 different types of amino acids which are joined to the protein backbone by peptide bonds. Amino acids are classified as polar, nonpolar, aromatic, anionic, and cationic. The amino and carboxylic groups in amino acids have weak basic and acidic characters, respectively. These groups are found in the ionized forms, arranging zwitterionic form of amino acids [9, 18, 19].

Proteins are essential macromolecules found in all living systems from bacteria to vertebrates and higher mammals. Over 50 percent of the cell dry weight can be proteins. Through covalent or non-covalent bonds, proteins can be attached to other biomolecules such as carbohydrates, lipids, phosphate groups, nucleic acids, flavins, and metal ions. Proteins are synthesized based on the information conserved in the genetic material of cells such as DNA. Replication, transcription, and translation are the main processes for synthesizing protein in living cells [18, 20, 21].

The proteins exhibit four types of structure including the primary structure (amino acid sequence), the secondary structure (conformation), the tertiary structure (overall folding of the polypeptide chain), and the quaternary structure (specific association of multiple polypeptide chains). The amino acids are connected through peptide bonds to form a linear sequence of amino acids, known as the primary structure. The secondary structure is obtained after the protein biosynthesis, where the supramolecular interactions such as hydrogen bonds and ionic, van der Waals, and π interactions arrange the local conformation of proteins. The secondary structure of proteins comprises mainly α-helices, β-sheets, and β-turns. The nature, bioactivity, and hydrophobicity of the proteins depend on amino acid compositions which is responsible for the folding of secondary structures into the three-dimensional tertiary structure. Nonlocal interactions, salt bridges, hydrogen bonds, and disulfide bonds cause stabilization of tertiary structure. In short, the secondary structure shows the spatial arrangement of neighboring amino acids in the peptide while the tertiary one explains the overall spatial arrangement of the protein. Non-covalent bonding into

the tertiary structures creates more complex assemblies known as quaternary structures. Several factors such as temperature, pH, organic solvents, and disulfide bond highly influence non-covalent bonds and disulfide bonds found throughout the secondary, tertiary, and quaternary structures. Consequently, these factors affect protein structures and functionalities. Based on functionality, protein can be categorized in several classes such as structural proteins and enzymes. Structural polypeptides act as the main constituent of feathers, hair, muscles, and silk to support integrity in the tissues and organs [9, 18, 22, 23]. Nowadays, proteins are used to develop many innovative and smart hydrogels. In the following sections, several protein and peptide-based hydrogels are explained.

3 Protein-Based Hydrogels

Proteins have been used attractively as raw materials to develop several biomaterials, for example, hydrogels, films, and composites. Hydrogels are produced in different forms such as cubic, hollow tube, rod, sheet, and film, considering their applications. Fibrous protein-based hydrogels offer similar structural, mechanical, and chemical properties to the native extracellular matrix, and these biomaterials can be processed simply under mild conditions to act in harmony with living cell. On the other side, proteolytic enzymes can degrade proteinous hydrogels. Such properties make them fascinating to be used in the field of tissue engineering [16, 24, 25]. To develop this kind of biomaterials, protein can be obtained from natural origin or prepared through biosynthetic routes. Peptides are also used to develop peptide-based hydrogels. The applied peptides are often chemically synthesized.

Protein can be converted to hydrogel using physical (cooling, heating, high pressure), chemical (acidification and addition of salt), or enzymatic treatments. Unfolding of the native protein structure and aggregation into a gel network is the most governing mechanism in protein gelation process. The formed network is able to hold water within its structure. The gel network can be stabilized through non-covalent cross-links such as hydrophobic and electrostatic interactions, and hydrogen bonds. Alternatively, a covalent cross-linking can stabilize the gel network [26, 27].

To modify mechanical strength and thermal stability of protein-based hydrogels, chemical cross-linking is carried out using many chemicals. Concentration of cross-linker influences hydrogel mechanical and release properties, as well as degradation rate. All proteins have the potential to be cross-linked, especially via amine and carboxylic acid functional groups. Amines are found at the N-terminus although lysine and arginine residues have additional amine groups. On the other hand, carboxylic acids are located at the C-terminus in addition to glutamic and aspartic acid residues. Other functional groups such as hydroxyl and sulfhydryl ones can be involved in cross-linking; but these groups are not abundant in comparison with amine and carboxylic acid groups. Protein-based hydrogels are often cross-linked by aldehydes and carbodiimides coupling amine-carboxylic acid. Both cross-linkers are toxic to living cells, so these compounds are not useful for cell encapsulation. To overcome this challenge, polyethylene glycol (PEG) with aldehyde or activated

ester groups is used for cross-linking. Remaining large amount of PEG in the hydrogel alters the properties of the gel, for instance it may increase the mechanical strength and swelling ratio. Genipin, a small molecule originated from gardenia fruits, is able to react with primary amines. It has been used to naturally cross-link several hydrogels based on collagen, gelatin, fibrin, and silk. However, carbodiimide and genipin are safer than aldehyde for cross-linking [28–30].

Whereas natural and synthetic hydrogels exhibited many limitations, development of hybrid hydrogels by combining natural polymers with synthetic polymers was emerged to customize chemical, physical, and biological properties of such hydrogels. The main approach to obtain hybrid hydrogels is grafting natural polymers with synthetic ones and vice versa. The grafted polymers can be cross-linked to form hydrogel network. Cross-linking a mixture of natural and synthetic polymer is another way to produce hybrid hydrogels. This kind of hydrogels can integrate the advantage of both synthetic and natural polymers to adjust physical properties, cross-linking ability, bio-adhesiveness ability, and biodegradability. In other words, chemical and physical properties of hydrogels can be adapted for particular applications with the conserving of biocompatibility, biodegradability, and functionality of the natural moiety. Nowadays, many proteins have been using to obtain hydrogels. In the next sections, the properties of collagen and gelatin, soy protein, silk, zein, keratin, casein, albumin, elastin, resilin, lysozyme, and peptides as well as their corresponding hydrogels are briefly described [17, 31–33].

3.1 Collagen and Gelatin–Based Hydrogels

Collagen as a natural polymer is found in extracellular matrices. Animal skin, bones, and articular tissues contain collagen and constitute about 30% of the total protein content in mammals. Collagens are mostly found in the fibrous form, and play important role in mechanical functions throughout the body. In connective and bone tissues, collagens offer biochemical properties needed for proper functioning. Furthermore, collagens reversibly interact with cellular mediators such as cytokines and growth factors. A triple helix including a repeat of amino acid sequence of -Glycine-Xaa-Yaa is the structural element of collagen, in which Xaa and Yaa often stand for proline and hydroxyproline, respectively. Collagen can be exploited in its native fibrillar form. The denatured collagens are suitable to fabricate several hydrogel forms such as sheets, tablets, pellets, and sponges [34–38].

Different animals such as cow and pig are used to extract collagen. The composition, solubility, transparency, mechanical strength, thermal stability, and rheological properties of collagen depend on the extraction sources. Gelatin is prepared by breaking triple-helix structure of collagen into single-strand molecules. Gelatin is thermo-responsive, and therefore it can display a sol-gel transition feature. Wherever dropping temperature occurs, the transition from solution to gel takes place. This change can be reversed by heating the mixture to physiological temperature. Gelatin-based hydrogels are nonimmunogenic, biodegradable, and biocompatible. Thus, this kind of hydrogels is known as an interesting candidate for biomedical applications.

The low thermal and mechanical stabilities of gelatin-based hydrogels can be improved by chemical modifications such as cross-linking. Gelatin-based materials have already been using in tissue engineering applications [39–43].

Collagen-based hydrogels can be prepared using physical treatments. Heating and increasing pH cause the aggregation of collagen through covalent bond to reform the fibrils and to create the hydrogel network. However, the derived hydrogels lack mechanical strength since collagen in native tissues has both intramolecular and intermolecular covalent bonds through lysine and hydroxylysine residues. Additional cross-linking is considered the main solution to overcome this challenge. Glutaraldehyde, genipin, carbodiimide, and gamma radiation have been used to cross-link collagen hydrogels. To customize the properties of collagen-based hydrogels, several materials were employed for the synthesizing of hybrid and composite collagen hydrogels. For examples, poly(N-isopropylacrylamide) and 2-methacryloyloxyethyl phosphorylcholine were used to produce such hybrid hydrogels. On the other hand, cellulose, hydroxyapatite, and silver nanoparticles have been applied to prepare composite collagen hydrogels [44–47].

3.2 Soy–Based Hydrogels

Soybean is a well-known food source, containing 40% protein. Glycinin and β-conglycinin are the main constituents of soy protein. This globular protein has proper gelling and foaming abilities, needed for preparing porous hydrogels. Open and interconnected pores, improved surface area, and high swelling capacity are features of the porous hydrogels. Soy-based hydrogels can be prepared using physical, chemical, or enzymatic cross-linking. The hydrogels prepared by thermal or cold treatments have weak mechanical structure and degrade fast. In contrast, chemical or enzymatic cross-linking can improve the structural strength. Chemical cross-linkers such as glutaraldehyde and genipin have been used to prepare soy-based hydrogels. Furthermore, zein and collagen in combination with soy protein isolates have been used to prepare the hybrid hydrogels. Soy hydrogels have been used for developing superabsorbents and biomaterials [44, 48–57].

3.3 Silk–Based Hydrogels

Silk proteins are extracted from the cocoons of silkworms, although the silk glands also contain these proteins. The composition and structure of silk proteins depend on silkworm species. Two classes of protein, fibroin and sericin, mainly constitute silk originated from silkworms. *Bombyx mori* fibroin has the repetitive sequence of a hexapeptide. This hydrophobic hexapeptide creates fibroin crystallinity and stability. Sericin is highly hydrophilic and consists of 18 amino acid residues. Sericin composition, solubility, and structural organization make it suitable for cross-linking, copolymerizing, and combining with the other polymers. Association of the crystalline regions with peptide domains increases the strength and elasticity of silk protein fibers;

therefore fibroin fibers can form films, sponges, gels, and tubes. Silk-based biomaterials can be applied in biomedical engineering because of their biocompatibility with living cells. Silk fibroin contains several hydrophobic amino acid residues like glycine, serine, and alanine. Consequently, it can form hydrogels using physical cross-linking methods such as temperature change, decreasing pH, and phase separation. The applied method and fibroin concentration influence gelation rate. For example, gel formation may occur faster with increasing the temperature or fibroin concentration. Hybrid silk-based hydrogels have been prepared using many natural and synthetic polymers such as alginate, chitosan, gelatin, collagen, and polyacrylamide. Genetically engineered silk proteins in combination with elastin-like polymers have been used to prepare silk-elastin-like polymers. Strength, immunogenicity, solubility, and degradation rate of silk-elastin hydrogels can be tailored with manipulation of amino acid compositions of both proteins. Repetitive silk peptides provide mechanical strength to the copolymer, while elastin peptides are responsible for flexibility, solubility, and cross-link density of the related hydrogels [58–69].

3.4 Zein-Based Hydrogels

Zein is a hydrophobic protein, found in the endosperm of corn kernel along with other proteins like glutelin, globulins, and albumins. Since zein is insoluble in water, solvents such as alcohol, anionic detergents, or urea are used to dissolve it. Zein can be self-assembled to several forms such as chains, layers, or foams via different processing methods. Zein is generally recognized as a safe biomaterial with the promising properties like biocompatibility, biodegradability, and non-toxicity. Because of low nutritional value, zein has great potential to be used as a precursor for the development of biomaterials. Particularly, zein-based hydrogels can be employed for manufacturing superabsorbents and drug delivery. For such applications, the zein should be solubilized in water, which can be performed through chemical modifications. For example, citric acid and acetic anhydride have been used to chemically modify zein, and the process is followed by electrospinning. The modified protein was soluble in neutral phosphate buffer solution. After cross-linking with sodium hexametaphosphate, the protein formed a hydrogel with stimuli-responsive behavior toward pH and ionic strength. Hybrid zein-based hydrogels can be prepared by combining with other polymers. For example, pectin–zein hydrogels have been developed by mixing a pectin solution with a zein solution in ethanol. Additionally, a solution of zein and soy protein isolates dispersed in soybean oil has been reported for the synthesizing of a hybrid zein hydrogel [70–80].

3.5 Keratin–Based Hydrogels

Keratin, a fibrous protein, is found in animal hairs, nails, wool, horns, and feathers, which can be divided into two groups of soft and hard keratin. Epidermal keratin is known as soft one, while hairs, nails, horns, and feathers are the sources of hard keratin.

α-Helix and β-sheet constitute keratin conformations. Keratin contains 14 types of amino acids with great amount of cysteine in its composition. For example, feather keratin and wool keratin have about 7% and 17% cysteine, respectively. As a result, many cross-links exist in the protein structure due to the formation of inter- and intramolecular disulfide bonds. Therefore, keratin is insoluble in water and has relatively high mechanical strength. Comparing with collagen, keratin is not degraded simply in vivo, since there is no keratinase in animal body to degrade keratin. Therefore, keratin-based hydrogels can be natural alternative to develop long-lasting biomaterials and superabsorbents [81–87]. Keratin is mainly extracted from wool, human hairs, and chicken feathers; all of them contain keratin more than 90% by weight. To synthesize the hydrogel, keratin solution should be cross-linked by a chemical agent or by promoting the formation of disulfide bonds. For example, H_2O_2 solution was added to keratin solution to stimulate the formation of these bonds. The resulting mixture was incubated over night to form gels. In another study, sodium bisulfite/potassium persulfate as the initiators were added to hydrolyzed feather keratin solution. Then, the protein solution was mixed with the mixture of methylenebis (acrylamide) and acrylic acid to prepare a keratin-poly acrylic acid hydrogel [82, 88, 89].

3.6 Casein-Based Hydrogels

Casein, the major proteinous constituent of milk, contains about 94% protein which is in combination with colloidal calcium phosphate. Cow milk has mainly four amphiphilic casein phosphoproteins. Casein hydrogels can be exploited in drug delivery systems because of interesting properties of casein such as high hydrophilicity, biocompatibility, edibility, and chemically modifiable structure. Disadvantages of casein may include its possible immunogenicity and allergenicity. Casein-based hydrogels can be prepared via chemical cross-linking by genipin in an aqueous environment. The mechanical strength of the cross-linked casein hydrogels can be customized by the amount of genipin. Enzymatic cross-linking is another approach to prepare casein hydrogels. Transglutaminase was used under mild conditions for gelation of milk proteins. The prepared hydrogel was suitable for biomedical applications. Hybrid casein hydrogels were also prepared through graft copolymerization using methyl methacrylate monomers. Furthermore, a pH-dependent hybrid hydrogel was synthesized using a mixture of acrylamide and methylenebis(acrylamide) with casein [90, 91].

3.7 Albumin–Based Hydrogels

Serum albumin is known as the most abundant globular protein in blood. It contains 580 amino acid residues. The protein consists of 54% α-helix and 40% β-sheet in its structure. Serum albumin acts as a transport protein for numerous molecules. Bovine serum albumin, with structural homology to human serum albumin, is an abundant and low cost globular protein with medical importance. Ovalbumin and

β-lactoglobulin are the other important albumins. Albumins have been used to prepare hydrogels or other biomaterials [36, 92–95].

3.8 Elastin–Based Hydrogels

Elastin, an extracellular matrix protein, gives tissues the properties of elasticity and strength. It is composed of about 800 amino acid residues, containing highly hydrophobic and cross-linking domains. Therefore, soluble forms of elastin including tropoelastin, α-elastin, and elastin-like polypeptides (ELPs) are frequently used to develop hydrogels. In addition, the elastin should be purified for biomedical applications. ELPs are referred to the polymers, the building blocks of which are synthesized in accordance with human elastin sequences. ELPs contain a pentapeptide repeat, Valine-Proline-Glycine-X-Glycine, in which X can be any natural amino acids, except proline. ELPs are thermally responsive, and can hydrophobically self-associate with increasing the temperature. ELPs do not stimulate immune system and are biocompatible. Thus these polypeptides have a great potential for application in drug delivery or tissue engineering [4, 36, 96, 97].

Chemical, enzymatic, and physical cross-linking approaches have been tested to prepare elastin-based hydrogels. For example, lysine-containing ELPs were rapidly cross-linked to form hydrogel by tris(hydroxymethyl)phosphine propionic acid. Clearly, the number of lysine residues in the peptide influences the mechanical properties of the hydrogel [96, 98].

3.9 Resilin–Based Hydrogels

Resilin, the most stretchable elastomeric protein, is found in insect cuticles. Resilin originated from dragonfly tendons can be stretched up to three times of its original length before breaking. The resilin-related gene in *Drosophila* encodes 620 amino acids. The expressed protein contains tyrosine and glycine residues which are responsible for cross-linking and flexibility of the polypeptide chains. Resilin-like hydrogels were generated by genetic engineering of resilin-encoding genes to be used as a support for drugs and enzymes. The resilin-based hydrogels were prepared by an enzymatic cross-linking method via horseradish peroxidase. In order to improve photochemical cross-linking ability, modification of the resilin by replacing tyrosine with phenylalanine was also reported. A hybrid hydrogel was produced by cross-linking of cysteine residues on resilin and vinyl sulfone-terminated PEG. Such hydrogels have been applied for biomedical engineering [25, 99–102].

3.10 Lysozyme–Based Hydrogels

Lysozyme, containing 129 amino acids, is a small globular protein with α-helix and β-sheet in its secondary structure. This protein is highly soluble in water and found in

egg white, animal tissues, tears, and milk. Egg white lysozyme cannot be self-assembled at pH 7. To overcome this challenge, dithiothreitol, a reducing agent is used to disrupt the disulfide bridges in lysozyme structure. This agent unfolds lysozyme and consequently induces the protein self-assembly. To form hydrogel at neutral pH, the solution of lysozyme and dithiothreitol heats to 85 °C and then cools slowly to room temperature [36, 90, 103, 104].

3.11 Peptide–Based Hydrogels

Peptides as well as proteins are often used in the development of hydrogels. The incorporation of peptides into biomaterials can be carried out with a high level of chemical specificity in contrast to proteins which often incorporate into biomaterials via nonspecific amine−carboxylic acid couplings. Peptide-based hydrogels show advantages for biomedical application such as binding ability to cells, growth factors and surfaces, and biodegradability [105].

Poly(aspartic acid) has several advantages such as hydrophobicity, biocompatibility, and biodegradability. It displays extensive potential applications in water treatment, cleaning products, and sanitary, agricultural, and biomedical fields. Poly (aspartic acid) hydrogels are synthesized by mild alkaline hydrolysis of the polysuccinimide gels. Poly(aspartic acid) hydrogels show a pH-dependent water absorption capacity [106, 107]. The gelation of poly(aspartic acid) can also be performed using co-polymerization, cross-linking, and radiation polymerization. For example, poly(aspartic acid) gels were prepared by chemical cross-linking polysuccinimide with 1,4-diaminobutane through a solid–liquid phase separation technique at cryogenic condition. In another study, cross-linking of this peptide using gamma radiation led to a high swelling ratio. A hybrid poly(aspartic acid) hydrogel was prepared by exploiting acrylic acid as a monomer, persulfates as an initiator, and methylenebisacrylamide and tetra-methylenebisacrylamides as cross-linkers. Furthermore, another hybrid hydrogel was prepared with combination of hyaluronic acid and polyaspartic acid. Other homo-poly(amino acids)s such as poly(lysine) and poly (glutamic acid) have also been applied to prepare hydrogels [108, 109].

4 Applications of Protein–Based Hydrogels

Protein and peptide-based hydrogels have many different applications in superabsorbent development, tissue engineering, and controlled release, which are described below.

4.1 Superabsorbent Hydrogels Based on Proteins

Superabsorbent hydrogels displaying exceptional water absorption ability are generally developed using ionic monomers which are lightly cross-linked. Water is

found in a hydrogel network in different forms. It can be free or bulk water present in the hydrogel exterior region being easily removable under natural conditions, water physically trapped into polymeric network called interstitial water, chemically bound water hydrating hydrogel functional moieties being directly attached to polymeric chains, and semi-bound water representing the form between the extremely bound and free water [14, 17]. Superabsorbent hydrogels are interestingly used as water-saving materials for agricultural uses especially for the revival of desert environment. Such hydrogels have the ability to reduce water consumption, to enhance fertilizer availability in soil and to help plant growth. Furthermore, superabsorbent hydrogels are widely applied as hygienic materials for instance disposable diapers and lady napkins to absorb blood and urine [110, 111]. Super-swelling hydrogels can be synthetic or natural-based. Natural superabsorbent hydrogels are mainly developed using polysaccharides or proteins. Cellulose, starch, and chitosan are examples of polysaccharides for preparing superabsorbent hydrogels [112–115]. Several proteins and peptides have been reported for developing superabsorbent hydrogels. Such hydrogels can be obtained by cross-linking of proteins after grafting with hydrophilic groups.

Collagen has been employed to prepare several hybrid superabsorbent hydrogels. As an efficient way to increase hydrophilicity, protein backbones were grafted with vinylic monomers and followed by cross-linking of the copolymer. For example, collagen and gelatin were used to develop such hydrogels, and a maximum water absorbency of 920 g/g was obtained using the hydrolyzed collagen-based hydrogel [116–118]. A collagen/kaolin-based hydrogel composite was synthesized through graft copolymerization of acrylic acid onto the protein. In this experiment, methylene bisacrylamide as a cross-linker and ammonium persulfate as an initiator were used. The maximum water absorbency was about 674 g/g [119]. Graft copolymerization of 2-acrylamido-2-methylpropane sulfonic acid and acrylamide into a hydrolyzed collagen in the presence of sodium montmorillonite was reported to prepare a superabsorbent nanocomposite. The optimum water absorbency was 681 g/g [120]. A hybrid hydrogel showing high swelling capacity was developed based on a mixture of kappa-carrageenan and gelatin via graft copolymerization of acrylamide. The hybrid superabsorbent hydrogel displayed a maximum water absorbency of 3310 g/g [121]. In another research, a superabsorbent hydrogel was developed by grafting a mixture of salep/gelatin with acrylamide. At the optimum condition, a maximum water absorbency of 762 g/g was obtained [122]. Recently, γ-irradiation in the absence of oxygen was employed to develop a hybrid superabsorbent hydrogel based on collagen–polyvinylpyrrolidone. A swelling capacity in the range of 2000% was obtained for this hydrogels at best [123].

Superabsorbent hydrogels containing –OH, $–NH_2$, $–CONH_2$, –COOH, and $–SO_3$ groups can adsorb many molecular and ionic species such as cationic dyes and metals [10]. Some of these groups are found in protein-based hydrogels, particularly in hybrid hydrogels. A hybrid superabsorbent hydrogel based on acrylic acid and the hydrolyzed collagen was synthesized through graft copolymerization. The hydrogel was able to uptake bivalent metal ions such as copper, cobalt, nickel, and zinc. It showed the highest affinity to copper ion, with a sorption capacity of 1.39 mmol/g,

while the maximum water absorbency was 500 g/g [118]. A poly(acrylic acid) was grafted into gelatin backbone to fabricate a granular hydrogel. The hydrogel was able to adsorb malachite green with the maximum adsorption capacity of 1370 mg/g [124]. A hydrogel based on gelatin, carboxylic acid functionalized multi-walled carbon nanotube and iron oxide magnetic nanoparticles was developed to adsorb anionic Direct Red 80 and cationic methylene blue dyes from aqueous solutions. The adsorbent showed a capacity of 465 and 380 mg/g for methylene blue and direct red, respectively [125].

Soy protein has been considered as a proper material to synthesize natural-based superabsorbent since it is easily available and cheap with highly hydrophilic character. Additionally, soy protein in combination with a plasticizer can be processed to form different shapes [126–128]. Manufacturing of cross-linked microcapsules as a novel catamenial absorbent using soybean protein through a solvent evaporation technique was reported. The hydrogel was able to absorb plasma up to 2000% [129]. In another study, soy protein isolate and potassium acrylate were used to synthesize a hybrid superabsorbent hydrogel. Primary amino groups in alkali-treated soy protein were functionalized using methacrylic anhydride by free radical copolymerization in a one-pot process. The functionalized soy protein had cross-linking ability [130]. A biodegradable poly-anionic hydrogel was derived through chemical modification of lysyl residues of soy protein isolate with ethylenediaminetetraacetic dianhydride as an acylating agent, followed by cross-linking with glutaraldehyde. The hydrogel was able to absorb water up to 300 g/g dry gel [15, 131]. Such a modification created a large number of carboxylate anions into the biopolymer [132]. As a result, numerous binding sites with hydrophilic character appeared. Acylating soy protein can also be performed with succinic anhydride. In order to obtain a superabsorbent hydrogel, succinic anhydride functionalized protein was mixed thoroughly with glycerol, and the process followed by molding the hydrogel. Water uptake capacity of the acylated hydrogel was higher than that of untreated protein [133].

A silk-based superabsorbent hydrogel was synthesized with graft copolymerization of acrylic acid and acrylamide onto the sericin chain in silk. Potassium persulfate and sodium sulfite as redox initiators and methylenebisacrylamide as a cross-linker were used. The hybrid hydrogel showed a maximum swelling capacity of 2150 g/g in water [62]. In the similar experiment, a synthesized silk sericin-g-poly(acrylic acid/attapulgite) hydrogel had a water uptake capacity of 1236 g/g [134]. Cryogels are macro-porous hydrogels formed below the freezing point of its solvent. Zein was used to prepare cryogels by graft copolymerization of acrylic acid onto the protein backbones, where acrylamide as a cross-linker and sodium bisulfite/potassium persulfate as initiators were employed. The absorption capacity of the cryogel for water and diesel fuel was about 120 and 50 g/g, respectively [79]. In another study, a sodium alginate/zein hydrogel was synthesized on a polypropylene fiber. The hydrogel assembly was able to extract polar compounds such as ethinyl estradiol, progesterone, and estriol [135]. Hydrolyzed keratin grafted by acrylic acid monomers was used to prepare a hybrid hydrogel in the presence of methylenebis (acrylamide) as a cross-linker and sodium bisulfite/potassium persulfate as initiators. The maximum swelling capacity of the hydrogel in distilled water was about 500 g/g dry hydrogel [82].

Several hydrogels based on renneted caseinate, sodium caseinate cross-linked with transglutaminase, and casein micelles cross-linked with transglutaminase were prepared, and their water holding capacities were investigated [136]. A physically cross-linked hydrogel composed of polyvinyl alcohol and casein was prepared via freezing–thawing treatment of aqueous solutions. Swelling ratio of the cryogel in water was about 14 g/g dry hydrogel [137]. A copolymer hydrogel, the blocks of which are based on elastin-like protein, was synthesized. The maximum cadmium binding capacity of hydrogel was 1.3 nmol Cd/nmol protein. The hydrogel showed reversibility in metal binding experiments [138]. A protein-based hydrogel system containing a network of engineered uranyl binding proteins and elastin-like polypeptides which was assembled through thiol-maleimide click chemistry was developed to enrich uranyl from natural seawater with great efficiency and selectivity [139].

The other proteins originated from fish, canola, and cottonseed were also used to develop protein-based superabsorbent hydrogels. Fish processing plants generate considerable amount of proteinous waste, which can be used for preparing superabsorbent hydrogels. A hydrogel based on fish protein was synthesized by introduction of hydrophilic groups into fish protein through modifying the protein with ethylenediaminetetraacetic dianhydride followed by cross-linking with glutaraldehyde. The hydrogel showed a water uptake capacity of about 200 g/g dry gel. Treatment of hydrogel with absolute ethanol increased the uptake capacity to 425 g/g [140]. In the similar experiment, the water uptake of a modified fish protein-based hydrogel was 540 g/g dry gel [141]. The synthesis of a canola protein-based hydrogel was reported through solution-based graft copolymerization of the canola protein backbones with acrylic acid monomers. In this reaction, methylenebis (acrylymide) and sodium bisulfite/potassium persulfate were used as a cross-linker and initiators, respectively. The maximum swelling capacity was 448 g/g dry hydrogel in distilled water [16]. A protein-based superabsorbent hydrogel was prepared through graft copolymerization of hydrolyzed cottonseed protein with acrylic acid. In the copolymerization reaction, methylene bisacrylamide as a cross-linking agent and potassium persulfate/sodium sulfite as the initiators were used. The hydrogel showed the maximum water absorbency of 890 g/g [112]. A cottonseed protein-poly(acrylic acid) copolymer hydrogel composite was synthesized to adsorb copper and lead ions from aqueous solution. In single component sorption experiments, the hydrogel composite showed sorption capacities about 3 mmol/g for each ions [142].

Peptides have also been used to synthesize superabsorbent hydrogels. For example, amino acid homopolymers such as poly(aspartic acid)s, poly(lysine)s and poly (glutamic acid)s are reported for developing such hydrogels. Ethylene glycol diglycidylether and polyethylene glycol diglycidylether were employed as cross-likers to synthesize poly(aspartic acid) hydrogels with super-swelling behavior [143, 144]. To improve swelling ability, several chemicals such as starch, carrageenan, and polyacrylamide were incorporated into poly(aspartic acid) hydrogels [145]. The modification of poly(succinimide)s with dimethylformamide resulted in allyl-containing poly(aspartic acid)s. The modified poly(aspartic acid)s were converted to hydrogels by chemical cross-linking, using ammonium persulfate/potassium

peroxodisulfate as radical initiators. Such hydrogels with low allyl group content offered water absorption capacity up to 424 g/g [146]. In another research, L-aspartic acid was used to modify starch, and the experiments were followed by hybrid hydrogel preparation. The resulting hydrogel was a superabsorbent with pH and temperature-responsive swelling behavior. The equilibrium water content of the hydrogel was more than 5000% [147]. To prepare lysine-based hydrogel, γ-irradiation on poly(lysine) aqueous solution was performed to lightly cross-link the polymer. The hydrogel showed a swelling capacity of 160 g/g. A hydrogel was also prepared by the γ-irradiation of poly(glutamic acid). The specific water content of this hydrogel was about 3500 g/g dry hydrogel. The results indicated that the hydrogel swelling capacity decreased when the irradiation dose increased [148]. Propyl esterification of the carboxyl groups of poly(glutamate) was employed to synthesize thermosensitive biopolymers. The poly(propyl glutamate) was formed hydrogel after cross-linking with hexamethylene diisocyanate. The maximum swelling ratio was 71% based on gel dry weight [149]. Recently, a superabsorbent hydrogel based on poly(glutamic acid) was synthesized through solution polymerization. Cross-linking was performed using ethylene glycol diglycidyl ether. Maximum swelling capacity in NaCl solution was 21 g/g [150].

4.2 Protein-Based Hydrogels in Biomedical Fields

Finding materials to mimic the native environment with the appropriate chemical and mechanical properties is a crucial challenge for tissue engineering and drug delivery. Hydrogels are able to mimic soft tissue since their properties can be modified through designating the nature of functional groups and controlling monomer and cross-linker concentrations before initiation of the gelation process [6, 58]. Hydrogels particularly proteinous one can be sensitive to the changes in environment factors such as pH, temperature, or metabolite concentrations and release their load in situ. It makes them useful as controlled-release delivery systems for bioactive agents [14]. On the other hand, proteins are one of the main constituents in the extracellular matrix. Consequently, polypeptides can be precisely incorporated into hydrogels, either by stable covalent bonds or through transient non-covalent interactions [6]. Protein-based hydrogels are known as promising biomaterials for many applications in the biomedical fields.

4.2.1 Tissue Engineering

Hydrogels are attractive for tissue engineering applications since they exhibit particular features. As a matrix, the advantages include their aqueous environment, the ability to transport biochemicals and to entrap living cells, and ease of modification and application [4, 151]. Collagen, the structural protein in the extracellular matrix, is known as one of the most applicable biopolymers for tissue engineering. In addition to inherent properties of hydrogels, collagen inserts excellent sites for attachment of adherent cells to the hydrogels, and displays in vivo biodegradability [33].

Collagen-based hydrogels were used to develop scaffolds for creating synthetic tissues such as blood vessel [152], spinal cord [153], cartilage [154], heart valves [155], and skin [156]. This kind of hydrogel is also applied for delivering bioactive factor to induce the chondrogenesis of stem cells [157, 158]. It is reported a collagen/hydroxyapatite hydrogel used as a scaffold for differentiation of stem cells to form bone in vitro and in vivo [159, 160]. The collagen sponges in combination with mesenchymal stem cells have been successfully applied to repair tendon defects in rabbits [161]. Collagen-based hydrogels are attractive in wound dressing applications because of their ability to temporarily repair damaged tissues [162]. A gelatin/alginate hydrogel cross-linked by carbodiimide, containing montmorillonite and kaolin, was used as bio-adhesives support. It may be applicable in hemorrhagic environment [163]. However, the applications of such hydrogels are limited because of the rapid degradation in vivo and low mechanical strength [164], which can be overcame by the appropriate cross-linking and hybridizing [165–168]. For example, an elastin-like polypeptide–collagen hybrid hydrogel was used as a polymeric matrix for encapsulation of mouse pre-osteoblastic cells. The results revealed high cell viabilities, cell attachment, and proliferation [168]. A reticulate matrix of hyaluronic acid hydrogel coated with collagen was employed as reconstructive tumor models for cancer researches [169].

Gelatin, derived from collagen, with nonimmunogenic, biodegradable, and biocompatible properties, are known as a candidate for tissue engineering. However, poor mechanical properties of gelatin enforce extensive cross-linking especially using tyrosinase and transglutaminase. Gelatin hydrogels were synthesized through enzymatic cross-linking with transglutaminase. The hydrogel characteristics such as cell adhesion, proliferation, and differentiation using an adipose tissue derived from stromal cells were evaluated in vitro. The results confirmed an improvement in the characteristics of the hydrogel [36, 170–172]. Gelatin-based hydrogels in combination with graphene oxide and carbon nanotubes have been used for cell encapsulation [173, 174]. A nanofibrous scaffold based on gelatin hydrogel containing bone-like apatite has been synthesized. The scaffolds showed an improvement in differentiation of the osteoblastic cells [175]. In another study, gelatin/alginate hybrid hydrogels containing hydroxyapatite were developed and used as a scaffold for bone and chondral tissue engineering [176]. A dextran/gelatin hybrid hydrogel containing a growth factor was used as a vehicle and controlled-release system for the differentiation of mesenchymal stem cells to nucleus pulposus [177]. Gelatin hydrogels prepared by cross-linking via lysine diisocyanate ethyl ester were developed. The results proved the biocompatibility of the hydrogels during in vivo study with mice [178]. Microspheres developed from styrene/gelatin hybrid hydrogel were loaded by growth factors and insulin. The beads were successfully applied for adipose tissue repair in rats [179].

A non-woven soy fiber was incorporated in a poly(vinyl alcohol) hydrogel through freezing–thawing cycles to manufacture a hydrogel scaffold. The results proved an increase in mechanical robustness of the hydrogel and cytocompatibility of the scaffolds for cellular attachment [180]. A fibroin hydrogel, inoculated with chondrocytes isolated from white rabbits, was synthesized and used as a scaffold to

evaluate its performance on connective tissue regeneration. The cells growth was observed in the fibroin hydrogel [181]. In another study, silk fibroin hydrogels were applied to treat bone defects in rabbits. The hydrogels showed biodegradability with no inflammatory effects. Bone healing and stimulated cell proliferation were also observed [182]. A hybrid hydrogel based on fibroin/sodium alginate has been developed to control mineralization of hydroxyapatite crystals in bone repair [183]. The use of a silk fibroin hydrogel as a scaffold to study adhesion and proliferation of human and animal cell lines was also reported [184–186]. Using a keratin hydrogel as a cell or growth factor delivery vehicle was described to regenerate functional muscle in the volumetric muscle loss injury in the rat [187].

Porous hydrogel scaffolds based on casein/bovine serum albumin were developed through the calcium-induced cold gelation technique. The scaffolds with cell adhesion and proliferation abilities were suitable for tissue engineering [94]. Bovine serum albumin was applied to develop a protein-based hydrogel. In vitro study proved the appropriateness of the hydrogel for tissue engineering since the prepared gels did not affect the viability of two cell models [93].

Development of highly cytocompatible and injectable elastin-based hydrogels with alterable gelation characteristics was reported. A thermoresponsive succinimide ester-functionalized copolymer was grafted with elastin through covalent bond formation. The prepared hydrogel was injectable and showed proper structural stability, mechanical properties, and live cell proliferation ability. The unique properties of the elastin-based hydrogel made it favorable for tissue engineering applications [188]. In another study, a photocross-linked elastin-like polypeptide gel was synthesized. The biocompatibility of the hydrogels was proved in vivo with subcutaneous implantation of hydrogels in rats. The hydrogel acted as a hemostatic material in vivo [189]. Hydrogels derived from elastin-like polypeptides were successfully used for treatment of articular cartilage damage, in vitro [190].

Other proteins such as resilin and lysozyme have also been exploited for hydrogel preparation. Preparing a resilin-based hydrogel using a modular protein was reported. The hydrogel was obtained by cross-linking the protein with tris (hydroxymethyl)phosphine and applied in cultivation of human mesenchymal stem cells. The results proved suitable cell spreading on the hydrogel [101]. In another research, a resilin-like hydrogel was successfully used to encapsulate human mesenchymal stem cells and aortic adventitial fibroblast cells [100, 191]. The lysozyme gels were used as scaffolds for culturing fibroblast cells. The results indicated proper cell proliferation and spreading [103, 104]. Additionally, application of soy-based hydrogels in orthopedics has been reported [49].

Protein domains, known as either distinct functional or structural units in a protein, are widespread in nature. These domains fold into three-dimensional structures and have been used as scaffolds for tissue engineering. For example, physical cross-linking of a triblock protein using leucine zipper coiled-coils to create cell binding scaffolds has been reported. Human cells were used to evaluate the hydrogel system. The results confirmed that the system was an attractive tool for developing cell-specific surface with tailored functional features [192, 193]. A synthetic hydrogel was obtained using a short building-block derived from the collagen sequence

through sol–gel polymerization. The hydrogel had the potential as a biomimetic scaffold for the stem cell proliferation [11].

Another peptide-functionalized hydrogel was synthesized through copolymerization of poly(ethylene glycol) diacrylates and methacrylated peptides. The hydrogel showed substantial affinity to human cells supporting its applicability in the field of tissue engineering [194]. A biocompatible and self-assembling peptide hydrogel was successfully developed as a cell carrier and scaffold for culturing nucleus pulposus cells [195].

4.2.2 Controlled Release

The delivery of the active agents such as drugs and DNA in a predetermined course of release is known as controlled release, which can occur in either sustained or targeted forms. In the field of drug release, providing adequate amounts of chemicals at a targeted area for known period is crucial [58]. Such a delivery is possible with the protein-based hydrogels.

Collagen has been applied as a delivery system. Collagen/fibrin microbeads were constructed and used as a delivery system for dental pulp stem cells in dental applications [196]. Mechanically robust soy protein hydrogels were synthesized with no cross-linkers. Drug releasing capability of the hydrogels was suitable using fluorescein. The hydrogel biocompatibility was proved through viability and growth of mouse fibroblast cells. The soy hydrogels were a promising biomaterial for drug delivery applications [50]. Silk-based hydrogels have been applied for sustained release of bevacizumab, a therapeutic for certain cancers [197]. Hybrid hydrogels based on fibroin/polyacrylamide have been evaluated for drug release. The results indicated that these hydrogels were applicable for sustained release of trypan-blue [198]. Since successful gene delivery is the key in gene therapy, several protein-based hydrogels were used as DNA delivery systems. For example, silk-elastin like polymers have been used as a DNA delivery system for cancer gene therapy [199, 200].

The use of a zein-based gelling system carrying pingyangmycin was reported. The drug was successfully released in vitro and in vivo [201]. In another study, a zein-based hydrogel loaded with doxorubicin was used for interstitial chemotherapy [80]. Fabrication of keratin hydrogels with tunable rates of erosion was reported for controlled release of a growth factor. The study proved the properness of the hydrogel for control drug and cell delivery [202].

Casein and polyacrylamide have been used to develop hybrid hydrogels to evaluate the releasing of bromocresol green. The results confirmed that casein had the potential to be used in the human body without any toxic effect [203]. A hydrogel with the potential for controlled release of hydrophilic drugs was prepared by cross-linking casein using oxidized hyaluronic acid containing aldehyde groups. In vitro cytotoxicity studies confirmed biocompatibility of the hydrogel [204].

A pH-sensitive hydrogel based on bovine serum albumin using hydroxyethyl methacrylate and acrylic acid monomers was prepared by gamma irradiation. The hydrogel showed high equilibrium swelling ratio up to 1550%. It was successfully

used for the release of flutamide [205]. In another study, a pH and redox sensitive albumin hydrogel was successfully used for in vitro tetracycline delivery under non-reducing and reducing conditions [92].

To enhance mechanical properties, a peptide-based hydrogel was synthesized through chemical cross-linking with genipin. The hydrogel loaded by naproxen showed its drug release ability in aqueous medium [206]. In another study, a pH-sensitive peptide hydrogel was developed as a biocompatible glucose-responsive insulin delivery system. The hydrogel was loaded with glucose oxidase, catalase and insulin. The peptide could self-assemble into a hydrogel form under physiological conditions. The system showed the ability to regulate the blood glucose levels in mice models [207].

5 Characterization Techniques of Protein-Based Hydrogels

Generally, there is a wide range of tests to detect and characterize the protein-based hydrogel, depending on their structure (such as the presence of nano-materials as filler or in the structure as crosslinker, etc.) and application types (behavioral change due to the environmental factors such as temperature, pH, stress or strain action, etc.). In this chapter, in order to identify the characteristics of the protein-based hydrogels, the characterization tests are divided into three parts: rheology, morphology, and thermal stability of protein-based hydrogel, as shown in Fig. 1.

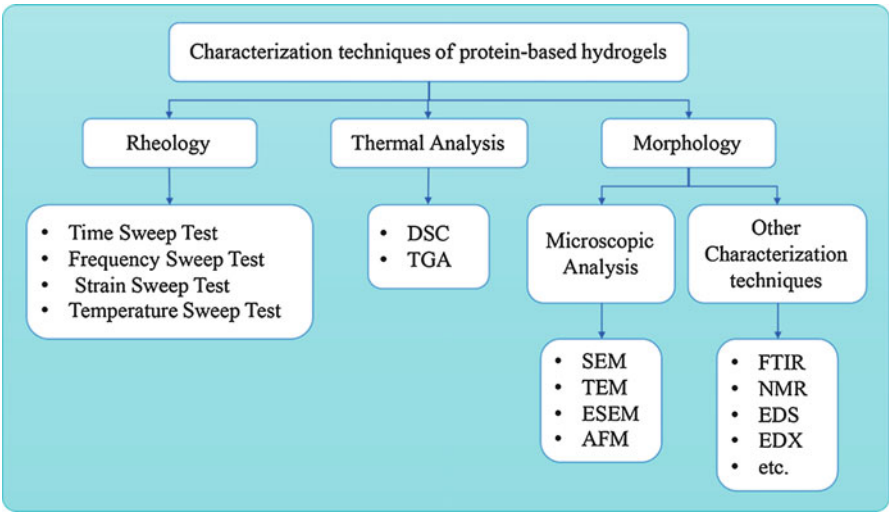

Fig. 1 A classification chart of characterization tests of protein-based hydrogels

5.1 Rheological Characterization of Protein-Based Hydrogels

When it comes to viscoelastic and low properties of hydrogels based on peptides, proteins, and polymers, rheological characterization can be the first significant candidate tool to cover more information. Moreover, rheology produces a straight view of different types and magnitudes of parameters effects (pH, salt, cations/anions, temperature, and enzyme) on the behavior of these hydrogels in various mechanical and biological environments. This part of this chapter proves the critical value of rheological characterization in order to configure the hydrogel characteristics such as gelation time, gel strength, viscoelastic character, and yield-strain behavior. Common rheological studies conducted on hydrogel materials include measurement of storage modulus (G', qualitatively the material stiffness), loss modulus (G'', qualitatively the material liquid-like low properties), and loss factor (tan (δ), the ratio of liquid-like behavior to solid-like behavior), all measured as functions of time, oscillatory frequency, and oscillatory strain. These studies on hydrogels can explain a complete tailor-made properties view on gelation kinetics, linear viscoelastic regions, and relaxation timescales.

The constant stress test is not suitable to analyze the rheological behavior of viscoelastic fluids because the results are not repeated in same conditions of subsequent tests. This unrecoverable results causes from two main reasons [208]. Firstly, the Wiesenberger effect, leading the fluid to rise from the rotary shaft (without discharging the contents of the container). Secondly, fluid resistance toward the flow, leading the constant stress, damages the natural network of the gel. Based on these features, oscillatory measurement instruments are most suggested to observe the gelation process with the aim of minimizing its effects on the severity of the reaction and without any influence on the three-dimensional gel structure. A common method to determine the viscoelastic property of material is the stress measurement along with sinusoidal alternate shear strain and a typical characterization method of viscoelastic gels is oscillation rheology. It is a technique to investigate the presence of reversible interactions and, by varying the frequency of deformation, the possibility of viscoelastic properties at various time scales. In an oscillation rheology measurement, sinusoidal shear deformation is applied and the resulting stress is measured as a function of time. The main parameters of the experiment are the amplitude of oscillation (γ_0) and the frequency of oscillation (ω, i.e., angular frequency) [209]. The correlation between strain (γ) and stress (τ) can be expressed as follows:

$$\gamma(t) = \gamma_0 \sin(\omega t) \tag{1}$$

$$\tau(t) = \tau_0 \sin(\omega t + \delta) \tag{2}$$

where δ is the phase difference between the two waves which is $\delta = 0$ for elastic solids and $\delta = 90^\circ$ for Newtonian fluids. Figure 2 shows a model of strain wave. If the material is viscoelastic, the phase difference will be in between of these two degrees. For proper implementation of test, the stress wave is usually divided into two waves with the equal frequency. One wave illustrates the elastic component (τ'),

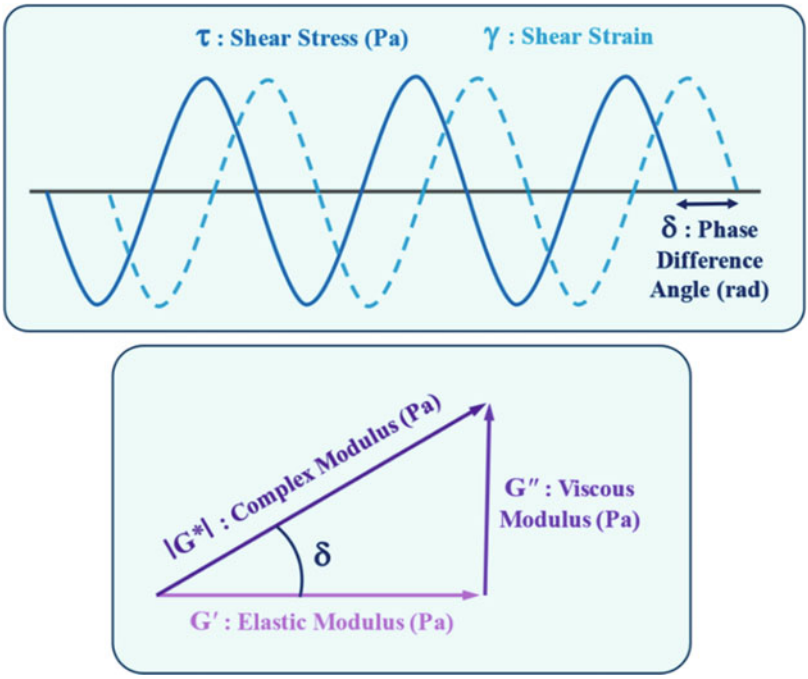

Fig. 2 A schematic of dynamic measurement

which has same phase of strain wave, and the other wave represents the viscous component (τ'') with a phase difference of 90 degrees (Fig. 2).

In an elastic solid, $\delta = 0$ or $\tan(\delta) = 0$ as G' dominates G'' completely. However, in a viscous fluid, $\delta = 90^\circ$ or $\tan(\delta) = \infty$as G'' dominates G' completely. In viscoelastic materials, $0 \leq \tan(\delta) \leq \infty$, depending on the time scale and temperature. When the viscous and the elastic behavior are equal to $\delta = 45^\circ$ or $\tan(\delta) = 1$, the material is making a transition from liquid to solid or the opposite [209–211]. According to Fig. 2, the storage modulus (the energy stored in the material) and the loss modulus (the energy lost in the material) can be described as follows, respectively:

$$G' = \frac{\tau'_0}{\gamma} \tag{3}$$

$$G'' = \frac{\tau''_0}{\gamma} \tag{4}$$

where τ'_0 is the maximum component of elastic stress. Thereafter, the equation for demonstrating the relation between phase difference, storage modulus, and loss modulus would be as follows:

$$\tan(\delta) = \frac{G''}{G'} \tag{5}$$

G'(Pa) and G''(Pa) are usually monitored as a function of time, applied angular frequency, and applied oscillatory strain. In a viscous solution, G'' is greater than G'. Moreover, the complex modulus (G^*) is defined [209] as follows:

$$G^* = \left(G''^2 + G'^2\right)^{0.5} = \mu^* \tag{6}$$

where $\mu^*$is the complex viscosity which can be related to the dynamic viscosity [210]:

$$\mu^* = \left(\mu''^2 + \mu'^2\right)^{0.5} \tag{7}$$

The above equations are recognized as the main relationships to study the rheological behavior of hydrogels.

Rheological tests of protein-based hydrogels can be explained in four categories to present comprehensive and separate characteristics. In general, rheological tests are divided into four parts time sweep tests, frequency sweep test, strain sweep test, and temperature sweep test (Fig. 1).

5.1.1 Time Sweep Test

These tests are applied with aim of start time of the reaction, elastic, viscose, and complex modulus at constant frequencies. Initially and in liquid state, as the reaction has not started, the viscous modulus is larger than the elastic modulus, and also tan (δ) > 1. After a while as the reaction starts of the process of formation of the material network, both the elastic and viscous moduli increase, but the elastic modulus shows a faster growth than the viscous modulus. In other words, the elastic properties transcend the viscous ones [212]. Meanwhile, as reaction continues, at special time at one point, the elastic modulus becomes greater than the viscous modulus (tan (δ) = 1), which results in two-curved collisions [204]. This point indicates the start time of formation of protein-based hydrogel structure [209]. Finally, after the collision point and to the end of the reaction, the value of the elastic modulus is greater than the viscous modulus (tan (δ) < 1) [213]. Besides, the amount of both moduli stay constant while the graph is smooth, indicating the completion of the hydrogel formation process [214]. Figure 3 shows the changes of elastic and viscous moduli of protein-based hydrogels schematically versus time. The transition from liquid to solid state and the gelation of the hydrogel is specified [215]. Moreover, the ultimate value of elastic modulus is an indicator to measure the protein-based hydrogel. For instance, G′ < 10 Pa indicates formation of weak gel which means the hydrogel has low strength. In addition, the gelation time of protein-based hydrogels could support their handling via injection [216]. In order to control the gelation process of the formed soy protein isolate (SPI) hydrogel proverbially and also to clarify the relationship between its property and network structure, the

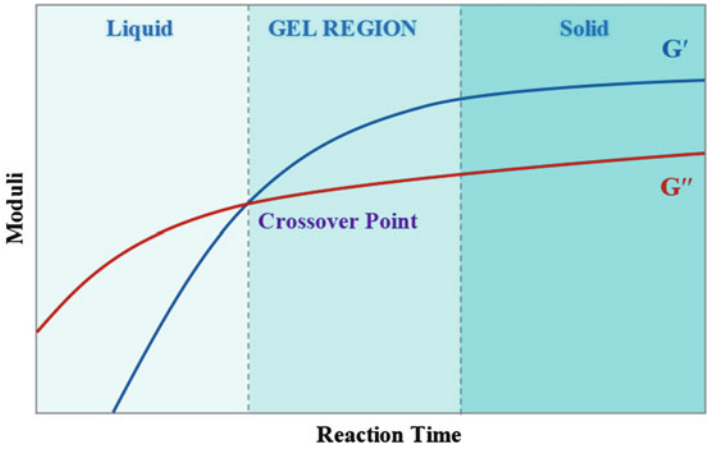

Fig. 3 A schematic of dynamic mechanical behavior along the gelation of the protein-based hydrogel

changes of viscoelastic properties versus time were monitored by the use of dynamic rheometry during the gelation process in the absence and presence of microbial transglutaminase (MTGase) [210]. In the absence of MTGase, the G″ value was larger than the G′ one in the investigated time range showing a dominant viscous property. In this case, gelation time was recorded as long as about 8 h. On the contrary, a crossover point between G′ and G″ was observed in the time range of introducing 0.1 wt % of MTGase into aqueous SPI system which was implied that there was a sol-gel transition. Beyond the crossing, the G′ value becomes larger than the G″ value, indicating that the system becomes more elastic. In this case, the gelation time (*t*gel) and the modulus at the G′/G″ crossover were found to be 15.25 min and 1.65 Pa, respectively [210]. It was found that the *t*gel value decreased with the increase of MTGase amount. The higher the MTGase amount, the shorter the gelation time was. Therefore, it confirmed further that the used MTGase had an obvious catalytic action for the gelation of SPI. For instance, in order to determine the group role of aldehyde at the gelation time of Casein-based hydrogel, time sweep test was used. Based on the crossover point curve, the higher the aldehyde group content or amount of used O-HA, the shorter the gelation time was. In other words, the in situ gelation took place more readily when a higher aldehyde group content or amount of O-HA was used. This may be assigned to the enhanced Schiff's base cross-linking in these cases [204].

5.1.2 Frequency Sweep Test

Frequency sweep tests are the moduli measurement tests as a function of frequency in order to show the hydrogel behavior at short timescales against long ones at constant strain. A critical feature of hydrogel characterization is the dependence of viscous and elastic moduli to frequency. At high frequencies (short timescales), a viscoelastic liquid system can display solid-like behavior, i.e., $G' \gg G''$, while at low

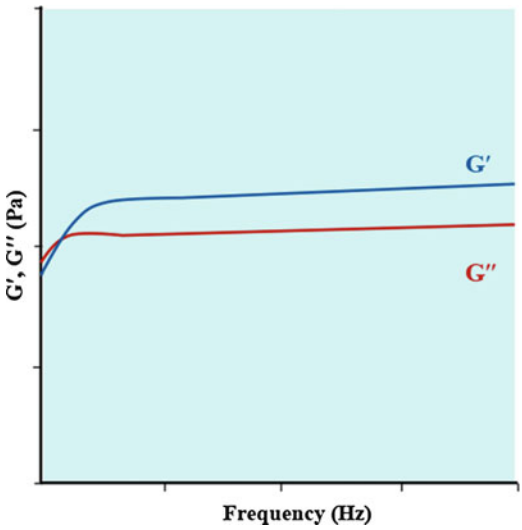

Fig. 4 The elastic and viscous moduli of protein-based hydrogel against the frequency

frequencies (long timescales), it can show liquid-like behavior, i.e., $G'' \gg G'$. Polymeric solutions with a concentration above the entanglement concentration, as well as entangled polymeric melts which are not chemically or physically cross-linked, show $G'' > G'$ (Pa) with a crossover point reached owing to increases in frequency after which $G' > G''$ (Pa). However, a solid, physical hydrogel will display solid-like properties ($G' \gg G''$) at all frequencies and timescales [217]. In order to ensure the formation of hydrogel structure, the elastic modulus is investigated under the frequency changes. The slope of the elastic modulus logarithm in terms of the angular frequency logarithm indicates the network formation of the hydrogel [218]. In other words, the absence of changes in the elastic and viscous moduli versus the frequency approves the formation of hydrogel structure [219]. Also, oscillatory shear tests and the resulting plots of G' and G'' are currently used to demonstrate the gel character, and to classify it as entanglement network or covalently cross-linked gel. It has been shown that covalently cross-linked gels exhibit an elastic modulus greater than the viscous modulus [123]. The illustrated curve in Fig. 4 shows the formation of three-dimensional network of protein-based hydrogel as the solution showed a rheological profile characteristic of elastic behavior with G' highly larger than G'' and almost frequency independent. The plateau storage modulus G'_{∞} value reflects the cross-linker density and strength. Hydrogels with a higher G'_{∞} value can potentially be obtained by increasing the building block concentration and/or using cross-linker proteins with a higher order of multimerization. For instance, G'_{∞} for the engineered disulfide-forming protein and its ligand) Tip1T58C-LE-$(H)_6$ hydrogel (is 262 ± 54 Pa, 15-fold greater than the plateau loss modulus G''_{∞} for the same gel (17 ± 1 Pa), consistent with gel-like materials [220]. Study of the elastic modulus change of SPI hydrogel in presence of MTGase shows that the elastic modulus has only a slight frequency dependence, demonstrating that the resultant SPI hydrogel has a rigid and elastic networks and is

physically stable. The good network stability of the formed SPI hydrogel could be attributed to the chemical cross-linking of SPI in the presence of MTGase, which might be advantageous for its controlled drug delivery and tissue engineering applications [210]. For example, to study the effect of laponite nanoplatelet (LAP) in regenerated silk fibroin (RSF) of *Bombyx mori* silk fiber, G′ and G″ of various RSF/LAP hydrogels as the function of frequency was investigated. It can be seen that the G′ of the RSF/LAP hydrogel increases from about 80 kPa to 200 kPa with the increase of the LAP content from 1% to 5%; and is much larger than that of pure RSF hydrogel (30 kPa). The results suggest that the incorporation of LAP in RSF can greatly improve the mechanical properties of the hydrogel [221].

5.1.3 Strain Sweep Test

An important property of the gel network is that its deformation degree can be determined without inflicting any defects in its network. Accordingly, strain sweep experiments were designed to measure the linear viscoelastic range (LVR) of the hydrogel. The LVR is an area in which no slip occurs between the layers and the hydrogel response is independent of the deformation magnitude while the hydrogel structure is maintained intact (unbroken). In other words, there is a linear relationship between the force applied and the observed deformation. Accordingly, by monitoring the moduli versus strain, the LVR for a given protein-based hydrogel can be determined [222]. The LVR is an outlet of applied strain values while G′ and G″ are independent of applied strain. Linear rheological measurements are classified as studies conducted within the LVR. Unlike LVR, nonlinear rheological measurements are obtained when experiments are performed outside of the LVR. In order to characterize materials in large and rapid deformations and also to have more complete view of responses of soft material against their processing, large-amplitude oscillatory strain (LAOS) measurements are critical, while steady-state shear is used to observe the low of hydrogels. The frequency sweep measurement and the oscillatory strain sweep measurement should be the first measurements to be carried out on the hydrogels during their rheological characterization [139, 223]. An accurate detail of frequency and strain response is important since during an oscillatory time sweep measurement by the rheometer the values of G′ and G″ will be under constant frequency and strains within the LVR condition. As Fig. 5 illustrates, changes in the elastic and viscous moduli of the hydrogel versus the strain changes show a viscoelastic behavior of the material. As it can be observed, at first, the elastic modulus of the hydrogel is higher than its viscous modulus (G′ and G″), and it keeps this superiority, in which this strain reflects the level of hydrogel's deformation (critical strain of the hydrogel). It should be noted that in this region, solid will have solid matter. The more strain increases, the more the hydrogel structure is broken down and the elastic modulus is reduced to less than the viscous modulus. In fact, less than 100% strain, the hydrogel will react to applied external forces and return the tension as much as possible to its original state [139]. To investigate the mechanisms involved in the formation and structure of the SPI hydrogels formed in the absence and presence of MTGase, strain sweep measurements were conducted for the cured hydrogel samples. For all protein concentrations, G′ remained almost constant as

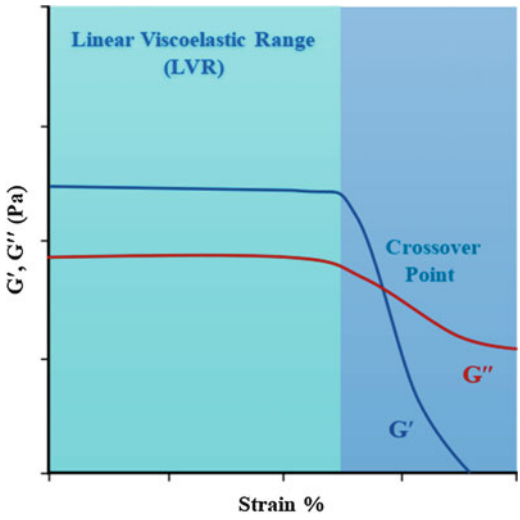

Fig. 5 The elastic and viscous moduli of protein-based hydrogel against the strain

strain increased and then suddenly decreased, indicating the bond breakage within the hydrogel network and a transition from linear to nonlinear behavior. With the increase of SPI concentration, the critical strain of the hydrogel value was found to decrease for the SPI hydrogel formed in the presence of MTGase and increase for the SPI hydrogel formed in the absence of MTGase [210]. For instance, by using strain sweep test, it is indicated that mechanical property of amino acid-based super-absorbent polymer hydrogel can be improved by copolymerization with flexible 2-(2-methoxyethoxy)ethyl methacrylate (MEO2MA) comonomer [224].

5.1.4 Temperature Sweep Test

Regarding the dependence of the hydrogel gelation time (the start time of the reaction) to temperature and the importance of temperature in the application of protein-based hydrogel, the investigation of the reaction start temperature, its effect on the hydrogel gelation time, and the limitation of the applied hydrogel temperature is considered essentially. Moreover, using this method shows the information related to the melting temperature indicating that the reaction is thermoreversible or not [103]. For this purpose, to maintain the three-dimensional structure of hydrogel, modifications of the elastic, viscous modulus, or complex modulus must be considered for the temperature of the hydrogels [219, 225]. It should be noted that the rate of increase in temperature in the rheometer, depending on the type of operational environment of the protein-based hydrogel, is applied to the hydrogel. In addition, the hydrogel gelation time can be determined versus time and temperature by checking the complex viscosity against time at various temperatures. The sudden increase point in viscosity represents the beginning of the gelation. In Fig. 6, the hydrogel state from viscous fluid to viscoelastic solids is illustrated versus temperature. For instance, in Fig. 6a, the collision point of the elastic and viscous modulus,

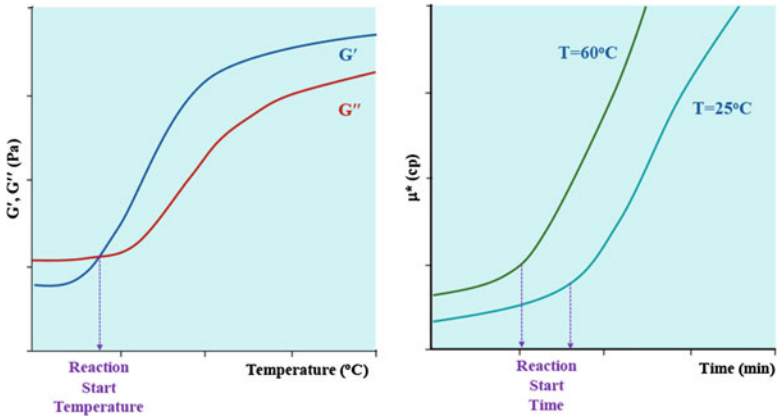

Fig. 6 The elastic and viscous moduli variation of protein-based hydrogel in face of time and temperature

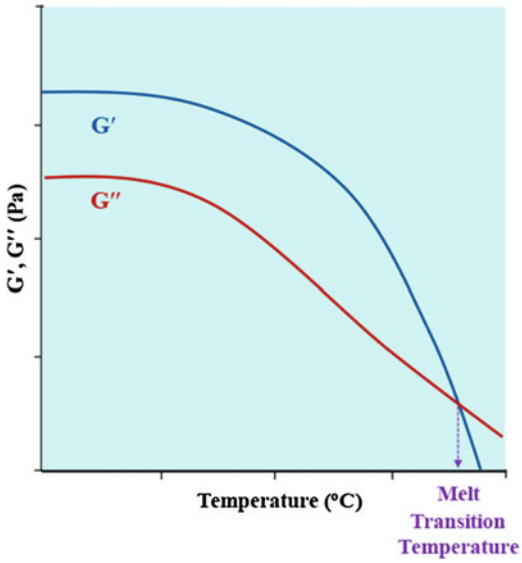

Fig. 7 The elastic and viscous moduli of protein-based hydrogel versus temperature

and the increase of G′ to G″, represents the reaction start temperature. Also in Fig. 6b, variations in the complex viscosity versus time at different temperatures indicate the endothermic reaction of the protein-based hydrogel of that example.

Figure 7 illustrate the modulus variation among temperature for the viscoelastic hydrogel. The melt transition temperature is assumed as the crossover point of both components of the dynamic modulus, or the sudden decrease in complex modulus G*.

5.2 Morphology Tests

5.2.1 Microscopic Analyses

The hydrogel pore size directly affects the rate of mass transfer between the hydrogel interior and the surroundings and is therefore a critical consideration for applications such as tissue engineering and biocatalysis [220]. In addition, a three-dimensional network can be detected using a scanning electron microscopy (SEM) image [11, 202, 206]. Therefore, investigation of the effect of different methods in the process of hydrogel synthesis and the size of the created pores in the porous structure would be possible by using micrograph images. Besides, the energy dispersive spectrometer (EDS) accessory can be also used to detect and determine a few elements in the hydrogel [221].

It should be noted that transmission electron microscopy (TEM) and scanning transmission electron microscopy (STEM) are two similar techniques that image the electron beam from the specimen [103]. TEM and STEM versus SEM have higher spatial resolution and additional analytical measurements. However, in these two methods, more precision is needed to build the sample [226, 227]. Moreover, the atomic force microscopy (AFM) test can also be used in the presence of nanomaterial in the structure of protein-based hydrogel to ensure nanoplatelets well disperse in the hydrogel matrix [93, 221].

5.2.2 Other Tests for Detecting and Characterizing the Protein–Based Hydrogel

The molecular structure of hydrogels has mainly been investigated using spectroscopic methods. Analysis of the polymers has been carried out using infrared spectroscopy, proton nuclear magnetic resonance (NMR) spectroscopy [108, 222]. Regarding the fact that the studied hydrogel of this study is protein-based, the presence of amide bonds within the hydrogel was expected. Therefore, Fourier transform infrared spectroscopy (FTIR) test is used as a suitable technique for protein-based hydrogel analysis [103]. An infrared spectrum represents the fingerprint of a protein-based hydrogel sample. Thus, infrared spectroscopy can be efficient in better identification (qualitative analysis) of hydrogel types. In addition, based on the size of the peaks in the spectrum, the amount of material available in the structure of the hydrogel can be investigated. Also, thermo-responsiveness of hydrogels was studied using a UV–Vis spectrometer equipped with a temperature controller [224].

5.3 Thermal Stability Analysis

The thermal analysis of the protein-based hydrogels was performed under differential scanning calorimeter (DSC) or thermal gravimetric analysis (TGA) [24, 82, 103, 180]. In order to measure the structural strength of protein-based hydrogel against temperature increase [130], the structural changes of the hydrogel to the temperature increase can be examined relatively with controlled state. In addition, the melting temperature and glass transition temperature are also measurable by this method.

6 Conclusions

All proteins have a potential to form hydrogel due to the presence of functional groups such as amino and carboxyl in their structure for cross-linking. Nowadays, several proteins and peptides have been used to obtain hydrogels. Collagen and gelatin are the most studied ones for hydrogel preparation. Physical, chemical, or enzymatic treatments can be applied to cross-link protein, which results in hydrogel formation. The preparation methods mainly depend on hydrogel applications. Physical hydrogels are reversible and sensitive to environmental conditions while chemically cross-linking causes stable structure in hydrogels. Glutaraldehyde is the most popular agent for chemical cross-linking, although it is toxic to living cells. Therefore, enzymatic cross-linking particularly using transglutaminase is preferred to obtain biocompatible hydrogels.

To develop protein-based superabsorbent hydrogels, proteins originated from soy, canola, cottonseed and chicken feather, and fish processing industries as well as zein and even collagen and gelation may be proper choices because of their low cost. Casein and egg white albumin seem to be used attractively in food industries for nutrient encapsulations. The other sources like silk, keratin, elastin, resilin, peptides and also collagen and gelation, showing proper biocompatibility, are applied in biomedical engineering. Sometimes, proteins should be chemically modified to obtain hydrophilic hydrogels and increase water absorbency.

Proteins can be employed individually or in combination with the other polymers and minerals, to develop hybrid and composite hydrogels, respectively. Hybridizing and compositing insert several features to hydrogels. For example, water holding capacity, mechanical stability, and rheological behavior are highly influenced by such combinations.

For practical applications, performing the rheological tests to find out the structural and thermal strengths, the effect of compositions on viscoelastic behavior, critical strain of protein-based hydrogels could be directive.

However, environmental challenges and the needs for sustainable development enforce the use of renewable, biodegradable, and biocompatible hydrogels. Proteins are a proper alternative for developing such hydrogels.

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Gelatin-Based Hydrogels

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Contents

Abstract

Hydrogels are crosslinked polymers that are able to absorb large amount of water, permit solutes within their swollen matrices, and provide sustained delivery of absorbed solutes. The use of various types of functional biopolymers as scaffold materials in hydrogels has become of great interest not only as an underutilized resource but also as a new functional material of high potential in various fields.

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Among them, gelatin has been considered as highly potential candidate to be utilized as hydrogel component because of its hydration properties such as swelling and solubility; gelling behavior such as gel formation, texturizing, thickening, and water-binding capacity; and surface behavior like emulsion and foam formation, stabilization, adhesion and cohesion, protective colloid function, and film-forming capacity. In addition, its properties of biocompatibility, low toxicity, antimicrobial activity, and biodegradability make it suitable for diversified biomedical applications. Many works have been reported in various scientifically reputable journals and publications worldwide that seem to have potential or satisfactory contribution of gelatin-based hydrogels. Numerous fields of application of gelatin hydrogels include, not limited to, usage as safer release system in agrochemicals, nutrient carriers for plants, drug and cell carrying devices, bioadhesives, wound healing, tissue engineering, etc. The purpose of this chapter is to compile the recent information on developments in gelatin-based hydrogel preparation, as well as new processing conditions and potential novel or improved applications.

Keywords
Gelatin · Hydrogel · Preparation · Application

1 Introduction

Recently a three-dimensional smart crosslinked polymeric network named hydrogel has gained considerable attention of the researchers. The characteristic properties of hydrogels such as desired functionality, enough smart response to the fluctuations of environmental stimuli (pH, temperature ionic strength, electric field, presence of enzyme, etc.), reversible swelling or shrinking and biocompatibility make them especially appealing to both materials and biological requirements [1–3]. Hydrogels based on natural or synthetic polymers have been of great interest regarding numerous fields of applications like biomedical engineering [4–7], tissue engineering [8–10], drug delivery [11], wound dressing [12], agricultural application [13, 14], pharmaceutical uses [15], food packaging [16], environmental applications [17], etc.

Hydrogels are not new but have been found in nature since life began on Earth. Many bacterial biofilms, which are extracellular matrix components, and plant structures are ubiquitous water-swollen motifs in nature [5]. Although less solubility, high crystallinity, unfavorable mechanical and thermal properties, unreacted monomers, and the use of toxic crosslinkers sometimes create barrier to the flourishment of hydrogel technology, the continuous development of new ideas to improve these properties with the combination of natural and synthetic polymers makes them a potential candidate in the field of biomedical applications. Different scientific approaches for the designing and processing of a specific hydrogel for a specific application are made to obtain maximum physicochemical properties, stimuli response, density, biodegradation, and biological and environmental response [5].

Both natural and synthetic polymers are now leading the field of source of hydrogels, but the use of the latter increases day by day. Among natural polymers, gelatin is one of the most common polymers to be used as structural networks of many hydrogels. It is a biodegradable natural polymer composed of different types of amino acids [18]. It is found in different parts of several mammals like cattle bones, pig skin, hides, and fish as well as in some plants and insects [19]. The structure of gelatin allows them to undergo interactions with other molecules and forms crystallites followed by further transformation into a three-dimensional network susceptible to immobilize the liquid [20]. Sometimes, chemical crosslinker enhances the gelation process through further networking [21, 22].

A wide variety of hydrogels made up of gelatin and other polymers have been reported yet in several scientific media [23–26]. This chapter attempts to summarize the recent development in this prominent field of polymer science. The first part of the chapter will briefly summarize the sources, structure, classes, and properties of hydrogels as well as their vast applications. Second part will emphasize on the structural properties of gelatin and gelatin-based hydrogels as well as their synthesis procedures. The third part will present most recent reports on the specific application of gelatin and modified gelatin-based hydrogels in different fields.

2 Hydrogels

Hydrogels are three-dimensional polymeric network which can take in and preserve 20 to 40 times, (even more in some cases) more water or biological fluids compared to their dry weight [7]. Hydrophilic groups in the polymeric network, either physically or covalently crosslinked with each other, become hydrated in an aqueous medium to form reversible hydrogel structure [27].

Based on the properties and application, hydrogels can be classified according to numerous ways and means. This classification depends on, sources of hydrogels, method of preparation, physical and chemical properties, ionic charges, swelling nature, biodegradation rates, and their nature of crosslinking [28]. In the following figure (Fig. 1), a detailed classification of hydrogels according to their different properties is stated.

Based on nature of the crosslink junctions of hydrogels, they can be mostly divided into two classes: physically crosslinked hydrogels and chemically crosslinked hydrogels. The polymeric composition of hydrogels directs to the development of some important categories of hydrogels. They can be classified as homopolymeric, copolymeric, and interpenetrating polymer network hydrogels. On the basis of their solubility, hydrogels can be classified into two groups in the water and enzymes. *Biodegradable hydrogels* have the capability of breaking down to simpler molecules, inside the body, with both water and enzymes. *Non-biodegradable hydrogels* are not broken down by the water and enzymes [29]. Hydrogels can be either “smart” or “conventional” based on their responses to unexpected changes in environment. Smart hydrogels are able to respond to external stimuli through sudden changes in the physical nature of the network. A small change in physical or

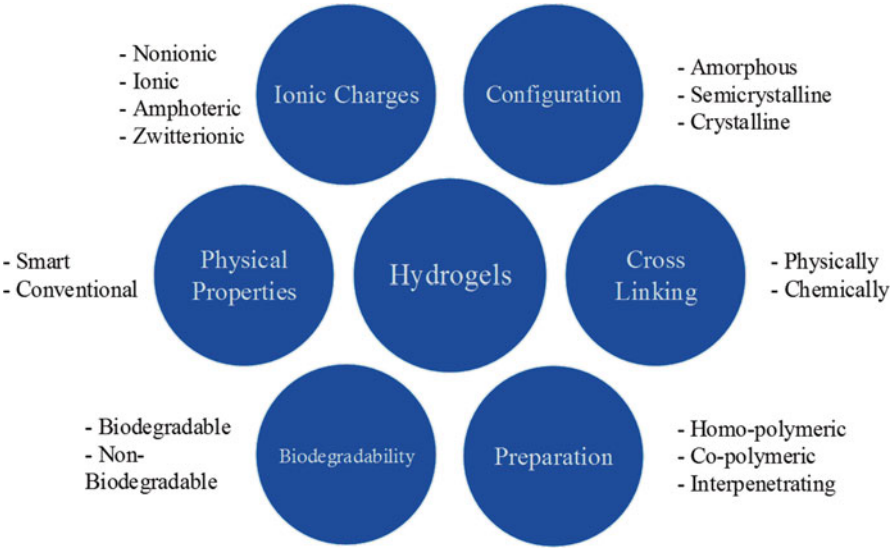

Fig. 1 Classification of hydrogels

chemical conditions can lead to a very sharp and large property change response. Physical and chemical stimuli include pH, light, pressure, ionic factors and chemical agents, temperature, electric, and magnetic field [30]. Conventional hydrogels do not show any kind of response to abrupt change in environment. Because of their distinct biocompatibility, physical properties, and flexible methods of preparation, hydrogels can be used in different areas. There are numerous amounts of original papers, research works, and reviews focused on the synthesis, properties, and applications of hydrogels. This section comprises the basic features and application areas of hydrogels.

2.1 Sources of Hydrogels

Hydrogels can be prepared from both natural and synthetic sources. The feasibility of use of hydrogels is still restricted due to their lower mechanical strength and fragile nature. As a result, to increase gel strength, service life, and water absorption capacity, natural hydrogels are gradually replaced by synthetic hydrogels [31].

2.1.1 Natural Hydrogels

Hydrogels formed from natural polymers can be classified into two main groups: polysaccharides and polypeptides. These hydrogels typically possess inherent biocompatibility and biodegradability. But, natural polymers are often expensive, and fine structural alterations of them are often limited because of their complex structures and delicate nature.

Polysaccharide–Based Hydrogels

As cellulose has abundant hydroxyl groups, it can be used to prepare hydrogels easily with fascinating structures and properties. Main advantages of these types of hydrogels are that they are environment friendly renewable polymeric materials with biodegradable property [32].

Chitosan is a cationic copolymer, which has hydrophilic character with capability of degradation results in biocompatibility and biodegradability, which make it a very useful source of natural hydrogels. These highly potential hydrogels have a great use in tissue engineering and drug delivery [33].

Alginate is a well-known biomaterial, and it will continue its application as one of the most significant one among the numerous biomaterials used for hydrogel formation. Properties like biocompatibility, biodegradability, and nontoxic nature and wide applications in drug delivery and cell delivery systems make it a great source of hydrogels [34].

Polypeptide-Based Hydrogels

Collagen is the main extracellular matrix material of human and animals. Hydrogels based on collagen have a great use in tissue engineering and biomedical applications. Transparent collagen hydrogels can be used as a corneal substitute for cornea regeneration. Other polymers can be incorporated with collagen hydrogels to increase its mechanical strength and lifetime [35]. Gelatin-based hydrogels have been evolving as great multifunctional biomaterials. It is an easily digestible protein that contains all the essential amino acids. The use of gelatin over collagen is increasing day by day because of its inexpensiveness and high dissolving capability in water. The gels formed from gelatin are naturally biodegradable and show non-cytotoxicity toward human cells [36].

2.1.2 Synthetic Hydrogels

Synthetic polymers are generally derived from monomers like acrylamide, vinyl acetate, ethylene glycol, and lactic acid. Because of their broadly variable and easily altered properties, synthetic polymer-based hydrogels have been extensively studied nowadays. The structures of these types of hydrogels can be regulated by changing the preparation techniques as well as physical and chemical compositions. Properties including swelling ability, mechanical strength, biocompatibility, biodegradability, stability, and porosity can all be adjusted for specific application purpose [31].

2.2 Mechanism of Hydrogels

Hydrogels are crosslinked polymer networks swollen in a liquid medium. The polymer network acts like a matrix to hold the liquid together, and the imbibed liquid serves as a selective filter to allow free diffusion of some solute molecules. Hydrogels may absorb water from 10 to 40% up to thousand times of their dry weights [37–39].

In structure formation of hydrogels, crosslinks act as an integral part. Crosslink is a bond which links one polymer chain to other and results in a stable network structure. Hydrogels can be characterized into two classes depending on the types of crosslink junctions: the physically crosslinked and chemically crosslinked [40]. Addition of crosslinks can change the physical properties of the polymer depending on the degree of crosslinks usage. The crosslinked polymer becomes elastic at limited crosslinks but becomes rigid at high crosslinks. Crosslinks also decrease the viscosity and melting point and increase the glass transition temperature, strength, and toughness [41].

Crosslinking is not accurately a property of hydrogels, as it is more of a cause of all the other properties of the material itself. Basically, every characteristic of a hydrogel can be correlated to the crosslinking degree [45]. The crosslinking can occur by ultraviolet irradiation, heating, or chemical crosslinking via crosslinker with a huge ensemble of reactions [42]. It is possible to tune the property of the material by controlling the degree of crosslinking and optimize it for any different applications [43, 44].

In addition, mechanical properties of hydrogels are very important especially from the pharmaceutical and biomedical point of view. The mechanical properties of hydrogels should be such that it can maintain its physical texture during the delivery of therapeutic moieties for the predetermined period of time. The desired mechanical property of the hydrogel can be achieved by changing the degree of crosslinking [37, 45, 46].

Above all hydrogels must be biocompatible and nontoxic in order to make it applicable in biomedical field. Biocompatibility consists basically of two elements: (a) biosafety, i.e., appropriate host response both systemic and local (the surrounding tissue) and the absence of cytotoxicity, mutagenesis, and/or carcinogenesis, and (b) bio-functionality, i.e., the ability of material to perform the specific task for which it is intended [37, 47].

2.2.1 Physically Crosslinked Hydrogels

This type of hydrogels is physically crosslinked and also known as temporary gels or thermoplastic hydrogels. The reason for physically crosslinked hydrogels to maintain their stability is the presence of reversible physical transient junction domains, associated with hydrophobic interaction, chain entanglements, crystallinity, hydrogen bonding, and/or ionic complexation [48, 49]. As the use of crosslinking agent is avoided in this type of hydrogels, that's why it is receiving a greater interest in recent years. Different methods have been investigated to create physically crosslinked hydrogels, like ionic interaction, hydrophobic interactions, hydrogen bonding interactions, etc. [30]. *Alginate* is a well-known example of a polymer that can be crosslinked by ionic interactions. It is a polysaccharide consists of mannuronic and glucuronic acid residues (β-D-mannuronate (M) and α-L-guluronate (G) monomers) and can be crosslinked by calcium ions. The three-dimensional network with hydrophilic structure of these gels can be illustrated by the "egg-box" model where each calcium atom is coordinated to the carboxylates and hydroxyl groups of four G monomers from two adjacent chains of the polymers (Fig. 2) [50].

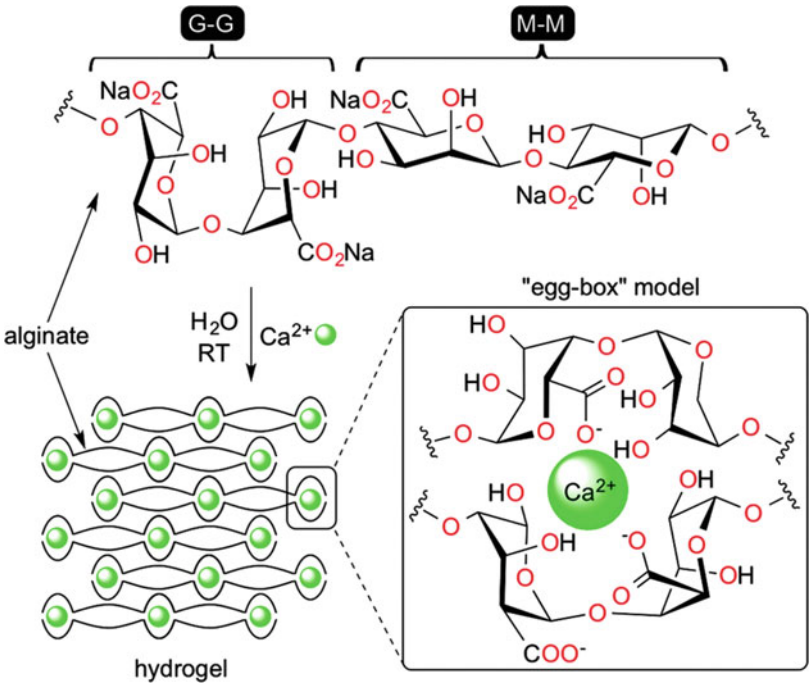

Fig. 2 Structure of the repeating units of sodium alginate (pK_a of carboxylic groups ~3 to 4) and formation of the hydrogel by coordination of Ca^{2+} cations between adjacent alginate chains as per the "egg-box" model. (Reproduced from [50]. Copyright © 2015, New Journal of Chemistry, Royal Society of Chemistry)

2.2.2 Chemically Crosslinked Hydrogels

Hydrogels that are chemically crosslinked are also known as thermosetting hydrogels. This type of networks has permanent junctions; that's why sometimes they are also called permanent gels [6]. Unless there is cleavage of the covalently crosslinked sites, they are not soluble in any solvents. Moreover, they cannot be successfully remolded or reheated after their initial heat-forming. Due to the lack of post-process modifications and process ability, benefit from chemically crosslinked hydrogels becomes limited [29].

Chemically crosslinked hydrogels can be formed by numerous techniques, like polymerization, radiation, small-molecule crosslinking, polymer-polymer crosslinking, etc. Radical polymerization of low-molecular-weight monomers like vinyl monomers in the presence of a crosslinking agent is a well-known method to generate chemically crosslinked gels (Fig. 3).

This type of hydrogels can also be attained by radical polymerization of polymers derivatized with polymerizable groups, i.e., macromonomer. UV-induced polymerization has been frequently used to prepare hydrogels in recent years. With this type of polymerization, patterned structures can be prepared. It should be kept in mind

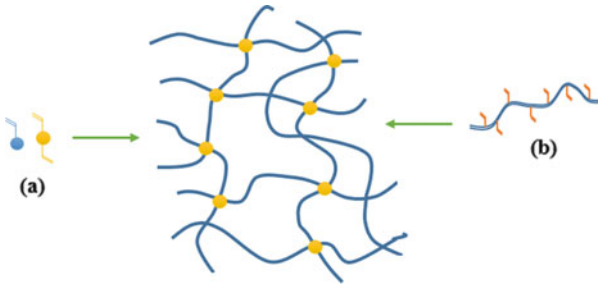

Fig. 3 Schematic diagram for formation of chemically crosslinked hydrogels by radical polymerization of (**a**) vinyl monomers and (**b**) macromonomers [30]

that the network structure might be affected if UV polymerization is carried out in presence of a drug [30].

2.3 Synthesis of Hydrogels

An enormous amount of works have been done and still going on to prepare novel hydrogels. Literature reveals that from preparation point of view hydrogels could be homopolymeric, copolymeric, and interpenetrating polymer networks (IPN). In this section, we will briefly discuss some of the preparation methods of these types of hydrogels.

2.3.1 Homopolymeric Hydrogels

Polymers that are derived from a single set of monomer/repeating unit are called homopolymers, which are the basic structural unit containing any polymer network [51]. Depending on the process of polymerization and the monomer nature, homopolymers may have crosslinked skeletal structure. Taking poly (2-hydroxyethyl methacrylate) (polyHEMA) as a monomer, polyethylene glycol dimethacrylate as crosslinking agent, and benzoin isobutyl ether as the UV-sensitive initiator is a one possible way to prepare homopolymeric hydrogel film. Prior to treating with UV radiation, the film was prepared in deionized water. In order to remove toxic and unreacted constituents that could harm living tissues, the film was immersed in water for 24 hours until it is fully saturated [37].

2.3.2 Copolymeric Hydrogels

When a polymer consists of more than one monomer/repeating unit, then they are called copolymer. Among these monomers, at least one must be hydrophilic in nature. These are arranged in random, block, or alternating configuration along the chain of the polymer network [52]. Using the mechanism of the ring-opening copolymerization of ε-caprolactone, the biodegradable triblock poly(ethylene glycol)-poly(ε-caprolactone)- poly(ethylene glycol) (PECE) copolymeric hydrogel can be synthesized for the improvement of drug delivery system. mPEG was used as initiator, stannous octoate as catalyst, and hexamethylene diisocyanate as coupling agent in the synthesis [53].

2.3.3 Interpenetrating Polymer Network (IPN) Hydrogels

This class of hydrogels is composed of two independent crosslinked synthetic and/or natural polymer components, contained in a network form. Generally, this type of hydrogels is synthesized by immersing a pre-polymerized hydrogel into a solution of monomers and a polymerization initiator. Thermodynamic incompatibility due to the perdurable interlocking of network segments is overcome, and limited phase separation can also be obtained in IPN method. It is believed that interlocked structure of the crosslinked IPN components can ensure the stability of the bulk and surface morphology [54]. To extend the functions of polyurethane (PU)-based hydrogels, Abraham et al. prepared IPN of PU and polyacrylamide (PAA) which could control water absorption. They mixed PU and PAA and then added the respective crosslinking agents, viz., vinylpyrrolidone and methylenebisacrylamide, followed by exposure of the mixture to UV radiation to obtain a hydrophilic hybrid IPN [55].

Because of hydrogels' extensive potential in wide range of applications, they have received much attention in the past 50 years [56]. Hydrogels' unique properties have made them ideal biomaterials for applications in cell encapsulation, drug delivery system, contact lenses, scaffolds for tissue engineering, biosensors, soft tissue replacement, intelligent cell culture substrates, wound dressing, and many more [57].

Hydrogels have been efficiently and effectively used in various biomedical applications because of its biodegradability and biocompatibility. As hydrogels mimic the natural tissues of the body, they have emerged as useful scaffolding biomaterials. For repairing tendon, ligament, cartilage, skin, blood vessels, and heart valves, both natural and synthetic hydrogels have been used as scaffolds in tissue engineering [58]. They are also used in wound dressings and as super-absorbent biomaterials due to their bio-adhesiveness [7, 21]. Synthetic hydrogels are suitable in the applications of contact lens, and some hydrogels have good transparency, high refractive index, and modulus which are essential for this product. PolyHEMA was the first hydrogel that has been used as a contact lens in 1960 [59].

The addition of the hydrogels to the surface of the soil can increase the water holding capacity of the soil and also can minimize the loss of nutrients from the soil [60]. The use of hydrogels as adsorbents for removing of heavy metal, recovering dyes, and removing of toxic components from various effluents has been studied. Adsorbents with carboxyl, sulfonic, phosphonic, and nitrogen groups on their surface favor metal ion adsorption [17].

3 Gelatin

Gelatin, a common, natural soluble functional protein compound having high interest and value, usually obtained by partial hydrolysis of the collagen which is the key fibrous protein element in the bones, cartilages, tendons, and skin, has the proficiency of forming transparent gels under certain conditions. Due to the variety

of the sources of collagen and extraction processes, gelatin illustrates a structure with changeable physical properties and chemical hybridism. Gelatin is exceptionally known for its unique gel-forming capability instead of some difference in the manufacturing techniques which ascertains it a worthy material for investigating the underlying functional properties in colloid studies [18].

3.1 Sources and Forms of Gelatin

There are different commercial sources of gelatin from which cattle bones, pig skin, hides, and fish are the primary ones. Special type of edible gelatin was extracted from edible Sudanese insects named melon sorghum bugs by Mariod et al. in 2011 [19]. However, mammalian gelatin is the primary contributor of the total world gelatin production, as well as fish gelatin provides a potential alternative. Plant sources are not available for gelatin, but gelatin can be obtained from seaweed extracts which is termed sometimes as vegetable gelatin.

3.1.1 Mammalian Gelatin

Connective tissues and bones of vertebrate animals are the primary element from where the mammalian gelatins are generated. Available sources of mammalian gelatin are pig skin (46%), bovine hide (30%), and pork and cattle bones (23.1%) [61].

However, researches on two different types of mammalian gelatins – bovine and pig sources – disclosed that both sources comprised of different components with wide distribution of molecular weight ranging from 10 to 400 kDa as well as the outcome established strong co-relationship between the average molecular weight and gel strength of the gelatin, with high isoelectric and melting points [62]. These two are usually required where health is concerned.

3.1.2 Fish Gelatin

From the name it can be assumed that the gelatin is obtained from the bones and skins of the fishes. This type of gelatin accounted about 1.5% of the total gelatin production which is increasing day by day showcasing the fact that the production of gelatin from alternative nonmammalian sources had grown in importance [61].

Apart from the well-known sociocultural and sanitary aspects, the researchers have the ascendant interest to optimize the extraction of gelatin from the by-products of fish industries in the last decades as an alternative source of gelatin [63].

One of the vital problems of fish gelatin is that it is less stable and has worse rheological properties than any of the mammal gelatins, and this may cause their applications limited. However this is only true for the reported cold-water fish such as cod, lumpfish, megrim, salmon, Alaska pollock, etc. Recent studies on tropical and subtropical water fishes such as tilapia, niger perch, catfish, etc. reported that they have nearly similar thermostability and rheological properties like mammal gelatins depending on the raw materials, pH, temperature, time, and other processing conditions [63–67].

3.1.3 Insect Gelatin

The insects can act as an interesting alternative source of gelatin. Mainly in Sudan, some edible insects are found such as *Agonoscelis pubescens* (sorghum) and *Aspongopus viduatus* (melon bug), and the oils extracted from them are highly used in cooking and some medicinal purposes. Thus the extraction of gelatin from these also took a great interest. Different types of extractions provide different amounts of yield like extraction using hot water showed up to 3% yield whereas mild acid extraction provided 1.5% yield. However, distilled water extraction gave only 1% yields. Melon bug gave high yield (about 1.45%) rather than the sorghum bug (about 1.3%). FTIR spectra of the obtained gelatins were similar with the commercial one showing the amide II bands around at 1542–1537 cm^{-1} [68].

From the researches, it is evident that aquatic source gelatins are similar in functionality like land-based gelatins [69, 70]. Both pork and fish gelatin have similar properties like gel strengths and melting points that follow the same trend with increased maturation time. However, due to the lower melting point of fish gelatin, it takes more time to reach the steady values. Both pork and fish gelatin shows the same pH stabilities, but NaCl depresses more readily in fish gelatin. Sucrose also has similar effects on both types of gelatin by increasing the gel strengths and melting points.

3.2 Structure of Gelatin

Understanding the chemical composition of gelatin is needed in order to explain the mechanism of gelation and other functional properties of gelatin. Numerous studies were carried out in this regard [71, 72], and most feasible result was based on the data of gelatin and ox-hide collagen using a wide variety of analytical techniques.

From the documentation, it was accepted that gelatin contains about 18 amino acids with 3 of them predominating in the structure. All these amino acids are linked together in a partly ordered fashion. About 1/3 to 1/2 of the total amino acid residues are glycine or alanine where glycine is the predominant N-terminal residue for alkali-processed gelatin and alanine stands for the acid-processed gelatin. Proline or hydroxyproline stands for ¼ of the amino acid residues, and about ¼ remains acidic or basic [18]. However, it was noticed that aromatic acid residues and "tryptophan" an essential amino acid have been missing from all types of gelatin compositions [73]. Changes in composition have also been observed during the change of the sources of gelatin. For example, whale or fish gelatin has larger amount of hydroxyamino acid serine and threonine compared to other land mammals.

Gelatin may contain small amount (~ 1%) of sugar. Depending on the sources and method of extraction, the nature, type, and amount of sugars vary. Till date five types of sugars have been documented (galactose, glucose, lactose, mannose, and xylose). They actually arise from mucopolysaccharides, a cementing substance and converted as amino sugar.

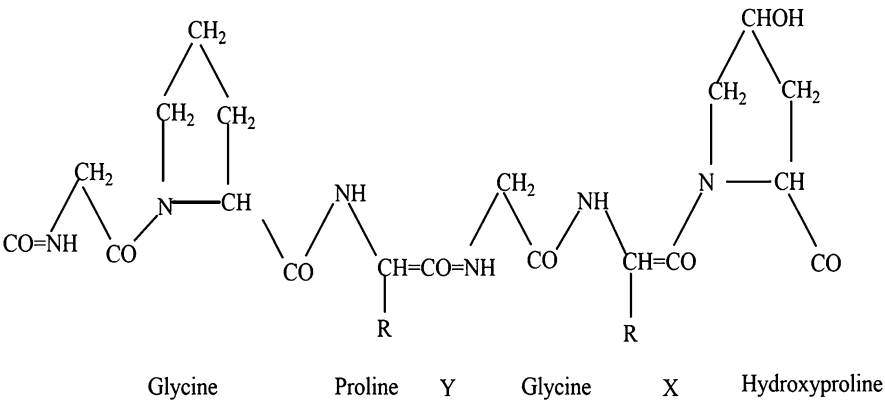

Fig. 4 Chemical configuration of gelatin

The real molecular structure of gelatin is still not clear till now, but arrangement of a small number of peptide fractions has been confirmed. A single-chain model consisting of repeating units of three amino acids in sequence -P-G-R where P is the proline/hydroxyl proline, G is glycine, and R is the side chain was first proposed by Astbury to elucidate a helical structure with the same sequences but that was omitted by Schroeder and Kroner as they speculated the sequence gly-pro-hypro-gly or gly-pro-hypro-gly-prohypro-gly which is the essential requirement of the structure of collagen. So, finally, gelatin is accepted as a linear chain with small branches as shown in Fig. 4 [18].

3.3 Properties of Gelatin

Gelatin is a biopolymer with keen interest based on mostly for its rheological and thermal properties. These properties diversify the application of gelatin.

3.3.1 Physical and Chemical Properties

Gelatin is very faint yellow to amber in color, and usually dry pure commercial gelatin is a tasteless, odorless, transparent, brittle, glass-like solid comprising a range of molecular weight about 40,000 to 90,000 Da.

It can establish the equilibrium both with acids and bases which can explain the nature of polypeptides and determine the amino acid composition due to the availability of amino and carboxylic groups on its backbone protein chain molecules and also help to unravel the structural stabilization and reaction nature toward other substances with it by using its ionization constant and electronically charged group.

Gelatin comprises several ionizable functional groups such as terminal α-amino and α-carboxylic groups, carboxylic and aspartic acid containing carboxylic groups,

the ε-amino group of lysine, the imidazolium group of histidine, and the guanidinium group of arginine. Isotonic point, which determines the dispersion and gelation as well as the use of gelatin in the food industry, is another most important property of gelatin, and it has been reported that the isotonic point of Type A gelatin is 7 to 9, whereas for Type B gelatin, it is about 4.8–5.1. Although gelatin is a water-soluble protein, the dispersion of gelatin must need some ample care. The dissolution process starts with the short time soaking of the granules in suitable amount of cold water and then increases the final temperature of the hydrated gelatin at about 35 °C either by continuous stirring and heating or by adding hot water to the system. Viscosity is another important property that varies extensively with the types of gelatin, temperature, time, and the concentration. However, the process of extraction also has an effect on it as acid-processed one generally possesses slightly higher intrinsic viscosity than the alkali-processed, but no difference had been found in the melting points.

Formation of gel, a vital process, does not have any clear concept. Several gelation processes of gelatin were recorded till date, but none of them can solely explain the mechanism clearly. A general idea being that the minute sections of gelatin undergo interactions and form crystallites which further turned into a ramified three-dimensional network susceptible to immobilize the liquid. This sol mixture finally resulted in the desired elastic solid or gel. The bindings in gel occurred by the implications of both hydrogen bonds and van der Waals forces as per the suggestions given by Ferry [20]. However another research concluded that the bindings were due to the peptide linkage [74]. Degree of acidity and speed of cooling time of the gelatin affects the properties of settled gels. Presence of acid lowers the liquefying temperature of a gel and increase the settling time. However, slow cooling speed permits the better orientation of the molecules within the gels. Gelatin is the rarest protein which is capable of forming good foams. Its sol can be cooled to 10 °C in order to obtain thick egg white consistency which is whipped to form foams.

Recently works has been focused on the properties of the film formed by gelatin as there are only a few experiments and results enlisted in the past on the film-forming ability of gelatin [75]. Gelatin, however, can form moisture impermeable edible films, and the properties like moisture content, water activity, and moisture barriers of these films have attracted the interest of the researchers. Due to the poor emulsifying properties of gelatin, it has a limited use in some sectors, but there is no certain method that has been worked out to improve this functionality till date. If this functional property can be improved, then it could be useful for multifunctional purposes in food and pharmaceutical industries. However, gelatin is capable to increase the viscosity of the continuous phase of an emulsion and thus can delay the flocculation and coalescence which improves the stability of O/W emulsions. The thermodynamic behavior of gelatin with acidic or neutral polysaccharides was difficult to understand because of the complex structure of individual polymers [76]. The pH and ionic strength of mixtures, ionogenic properties of gelatin, and gelatin-solvent interactions are responsible for the degree of interaction of gelatin with other biopolymer.

3.3.2 The Biological Activity of Gelatin

Although gelatin has some beneficial biological functions in food and pharmaceutical industries, the biological activity of gelatin has been reported as zero as per [73] because it lacks an essential amino acid "tryptophan" which is vital for a biologically completed protein, i.e., gelatin cannot provide a complete set of amino acid essentially required for the synthesis of protein.

Functional components can be entrapped by gelatin as a carrier and thus provides protection against oxidation or degradation in the time of storage as it can form complex with anionic polymer in the form of microcapsule. This is used when bioactive packaging is ingested in the body.

3.4 General Application

Every year a large amount of gelatin has been used in the food industry especially in making desserts, candies, jellied meat, ice creams, bakery goods, and dairy products as clarification agent, stabilizer, thickener, emulsifier, texturizer, and protective material [20, 74]. Due to the surface-active properties of gelatin, it has also find its use as a foaming, emulsifying, and wetting agent in pharmaceutical, medical, and technical applications.

3.4.1 Food Industry

Due to its high content and protein, gelatin is widely used in the food additives or in healthy food. Gelatin possesses the unique hydrocolloidal property which makes it applicable in the numerous food industries. The major classical uses of gelatin are in clarification and stabilization. Gelatin removes turbidity of a solution by flocculation and sedimentation and thus brings the clarity. So, it is highly used in drinks and beverages containing tannins. Tannins react with gelatin to produce sediment as a form of tannin-gelatin complex. The amount of gelatin in clarification process should be accurate; otherwise over gluing or stabilization of colloidal matter may occur due to the excessive amounts or insufficient amounts of gelatin.

Around half of the edible gelatin in food industries is used for the preparation of desserts including food toppings, pastry toppings, etc. While using gelatin in desserts, the pH should be maintained between 3 and 3.5 for palatable tartness. Due to the foaming ability of gelatin, it is also used in the manufacture of marshmallows, a colloidal dispersion of gas within a liquid.

Gelatin is extensively used in pies, breads, and cakes as a setting agent, stabilizing substance, or foam-forming materials. It is also used in the meat industry especially in the preparation of bone-cooked hams, sausages, cheese, canned hams, and meat jellies as coating agents. Gelatin can also be used in frozen fruit puree and frozen turkey products. Due to the high swelling and water-binding capacity, gelatin impairs juiciness in frozen fish or meat product and thus reduces drip loss.

3.4.2 Pharmaceutical Industry

In developed countries, almost 10% of the edible gelatin is used in pharmaceutical industry especially in capsules and emulsions. Although the biological value of gelatin is zero, it has several surgical and serological characteristics and thus produces some oncotic effects and can be used in the preparation of plasma substitutes. Highly purified gelatin hydrolyzates are often co-administered with products to compensate calcium deficiency in pregnancy, adolescence, and lactation, or it can be used to treat calcium deficit associated with osteoporosis in the elderly [77]. Methionine and cystine from derived gelatin are carrier of sulfur, and that's why they are beneficial in treating connective tissue diseases like scleroderma, rheumatoid arthritis, etc.

Currently, gelatin hydrogels made progresses in the sector of bone regeneration and also emerge as a surgical tool for skull defect repair and reconstruction of skull base [78]. Gelatin is also used as injectable biomaterials for one surgery, oral capsules, breath freshener microcapsules, oral dissolvable medicaments, cosmetics, prosthetic heart valves for intravascular applications, and as raw materials for artificial skin [79–81].

3.4.3 Photographic Industry

For processing of exposed film material, gelatin emulsions have been thoroughly used as a component in a photographic developer as it enhances the capability of a developer to distinguish between exposed and unexposed crystals. It is the best medium for photographic emulsions and has been continuously improving the quality and speed [82].

3.4.4 Other Uses

Gelatin also finds some other uses which are summarized below:

- It is used as a carrier or separating agent of some other materials like β-carotene. It makes β-carotene water-soluble.
- It works as a binder between match heads and sandpapers.
- Hydrolyzed collagen is a non-gelling variant of gelatin which is broadly used in the cosmetics.
- It is also used as an external surface-sizing material for papers.
- Unrefined gelatin is used in manufacturing glue, i.E., hide glue.

4 Hydrogels from Gelatin

4.1 Synthesis of Gelatin-Based Hydrogels

In general, based on the various available forms (e.g., solid molded forms, pressed powder matrices, microparticles, coatings, membranes, etc.), hydrogel network can be fabricated by molecular entanglements and/or through secondary forces including ionic, H-bonding, or hydrophobic forces. Many natural and synthetic polymers are

capable of forming physical and chemical hydrogels. Physical homogeneous hydrogels are characterized by some physical interaction rather than chemical bonding, while chemical hydrogels mainly consist of covalent bond in presence of a crosslinker. But sometimes chemical crosslinker is not the major element to form chemical hydrogels. Gelatin is an amphipathic polymer, capable of forming chemical hydrogels in presence of crosslinkers. On the other hand, simple dissolving of gelatin in hot water and then cooling down to below the room temperature will form a physical gel of gelatin [21]. However, this type of physical hydrogel is not stable at body temperature and does not allow researchers to control and fine-tune its properties [83]. This is one of the drawbacks that have led to introduce chemical hydrogels of gelatin by crosslinking without prior modification and/or after functionalization of its side groups. Unmodified gelatin can be crosslinked in various ways to form a covalent network, such as by chemical or enzymatic crosslinking [26].

Considering the reaction techniques to form physically and chemically crosslinked hydrogels, several distinct techniques have been followed for decades. Radical polymerization, crosslinking with aldehydes, crosslinking by addition and condensation reaction, crosslinking by using radiation and enzymes, etc. are some of the most popular ways to form chemical gels. Of these, crosslinking with aldehydes and condensation reaction technique are the two most important pathways to form gelatin-based chemically crosslinked hydrogels [22].

For the last few years, many researchers have exhibited their interest in developing various gelatin-based hydrogels, because of its multifunctional prosperities and easygoing preparation methods. Some of the synthesis techniques of gelatin-based hydrogels are stated in the following subsection starting from 4.1.1.

4.1.1 Gelatin–Methacrylate Hydrogels

As a part of the chemical modification (or functionalization), methacrylic anhydride is widely chosen over other modifiers [26]. This reagent has been found to synthesize hydrogel with pure gelatin by Yue et al. By a direct reaction between gelatin and methacrylic anhydride in phosphate buffer, a substitute group gelatin methacryloyl is formed at 50 °C. This reaction introduces methacryloyl substitution groups on the reactive amine and hydroxyl groups of the amino acid residues. This gelatin methacryloyl undergoes photo-initiated radical polymerization (i.e., under UV light exposure with the presence of a photo initiator) to form covalently crosslinked hydrogels. This kind of hydrogels is suggested to be applied in biomedical field (Fig. 5) [84].

One recent example is the development of gelatin methacrylate (GelMA) hydrogels where the hydrogel is synthesized by adding methacrylate groups to the amine-containing side groups of gelatin, which becomes a photo-crosslinkable hydrogel [85]. The author has proposed the use of photo-crosslinkable GelMA hydrogel as a permissive biomaterial for the formation of functional vascular networks. A different study conducted by Jason et al. demonstrated that gelatin methacrylate hydrogel was fabricated from methacrylated gelatin macromer (by using methacrylic anhydride) which in turn crosslinked to get the final hydrogel.

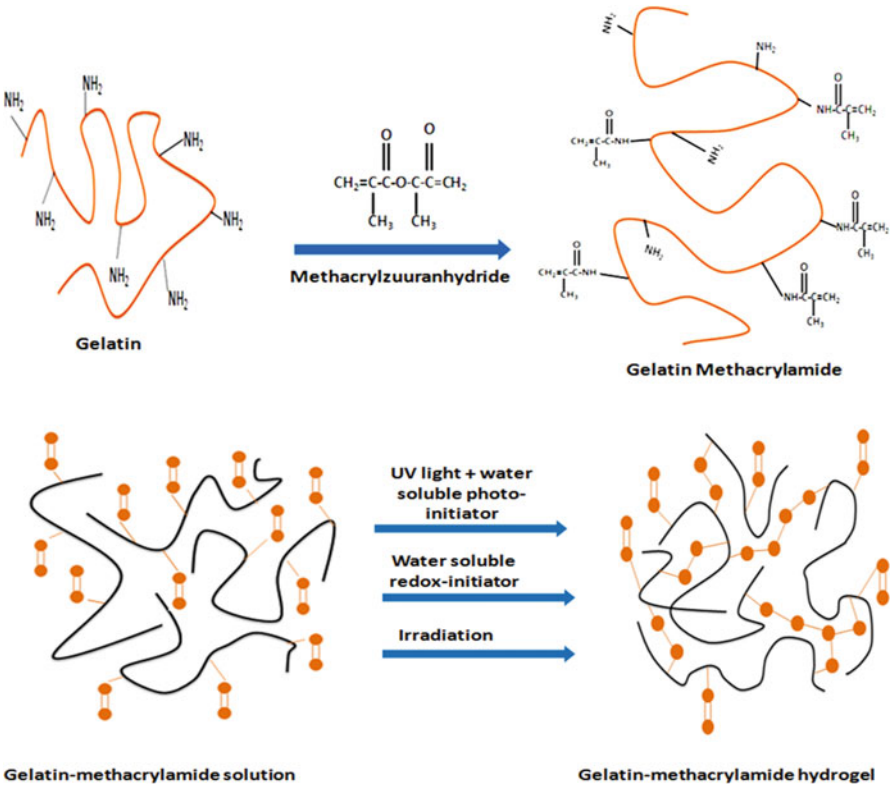

Fig. 5 Chemical modification of gelatin with methacrylamide side groups [91]

Rather than being applied as a functional vascular network, this type of hydrogel is highlighted for its application in microscale tissue engineering and as an attractive material for cell-laden microtissues [86]. The application of this hydrogel can also be selected by controlling some of the condition during its fabrication. For example, high degree of methacrylation (low biodegradability) during macromer preparation results its application to fabricate organized vasculature within engineered tissue constructs which is able to create platforms for drug and cytotoxity and basic biological studies [87]. However, immobilized inorganic-organic phase is also desirable for implant application. Focusing on this point, gelatin-methacrylated hydrogel-hydroxyapatite composites were synthesized by photochemical grafting which is followed by biomimetic mineralization and finally a covalent immobilization on titanium substrates. This kind of material is expected to be used for bone regeneration and repair not only on titanium substrate but also for many metallic, steel, and other polymeric substrates [88].

Similar crosslinkable hydrogels are fabricated by Salamon et al. without further photolytic crosslinking which is used for promoting in-vitro chondrogenic differentiation of human mesenchymal stem cells [89]. Another study conducted by

Loessner et al. stated the use of gelatin methacryloyl-based hydrogels as modular tissue culture platforms [83]. Again, gelatin was chemically modified with methacrylamide side groups which could be further polymerized by radical initiators or high energy irradiation. The methacrylamide side groups are introduced by reaction with methacrylic anhydride with the ϵ-amino groups of lysine residues [90]. Besides using this hydrogel solely, a hydrogel composite can be fabricated by embedding multipotent stromal cells (MSCs) and cartilage-derived matrix (CDM) particles into the prepared hydrogel. This kind of hydrogel composite was fabricated by Visser et al. which ultimately showed its application in the field of endochondral bone formation [91].

Besides using pure gelatin as a raw material for hydrogel fabrication, recombinant gelatin can also be used for sustained release of the proteins. This is also a pathway to make chemical gel through a chemical crosslinker. Here the recombinant gelatin is modified with methacrylic anhydride, and the product obtained upon methacrylation reaction acts as a crosslinker to form the desired hydrogels. After dissolving the modified gelatin, centrifugation was performed, and the final addition of potassium peroxodisulfate and N,N,N′,N′-tetramethylethylenediamine into the mixture helped to induce crosslinking of gelatin methacrylate residues to obtain the final hydrogels [92]. It is to be noted that to obviate the drawback of gelatin-based physical gel for being less stable at body temperature, gelatin has been chemically functionalized with unsaturated methacryloyl groups to result in gelatin methacryloyl, which forms covalently crosslinked hydrogels by photo-initiated polymerization under mild conditions [83].

4.1.2 Gelatin-Dextran Hydrogels

Several works have been published based on the aldehydes as the crosslinker in forming hydrogels from gelatin. For example, in a study of Draye et al., a hydrogel film was fabricated by using gelatin as a main raw material and dextran dialdehyde as a crosslinking agent. Here a 20% oxidized dextran dialdehyde was used as a crosslinker, and then gelatin is added to make the 1-mm-thick hydrogel film. Crosslinking between gelatin and dextran dialdehydes was executed by the production of Schiff base links between free ϵ-amino groups of the lysine and hydroxylysine residues present in gelatin and the aldehyde groups in case of oxidized dextran [93]. Vandenbulcke et al. have reported on the preparation of gelatin hydrogels crosslinked with partially oxidized dextrans (Fig. 6) [94].

4.1.3 Gelatin–Chitosan Hydrogels

Chitosan is considered as an excellent biopolymer due to their physicochemical and biological properties. Chitosan dissolves readily in acidic environment (pH below 6) which can be retained by crosslinking through various agents, e.g., glutaraldehyde, glyoxal, or epichlorohydrin [95]. However, a derivative of chitosan is carboxymethyl-chitosan (CM-chitosan) that showed better solubility profile as well as nontoxicity, biocompatibility, biodegradability, and low-immunogenicity [96]. CM-chitosan hydrogels were found mechanically weak. For this reason, gelatin

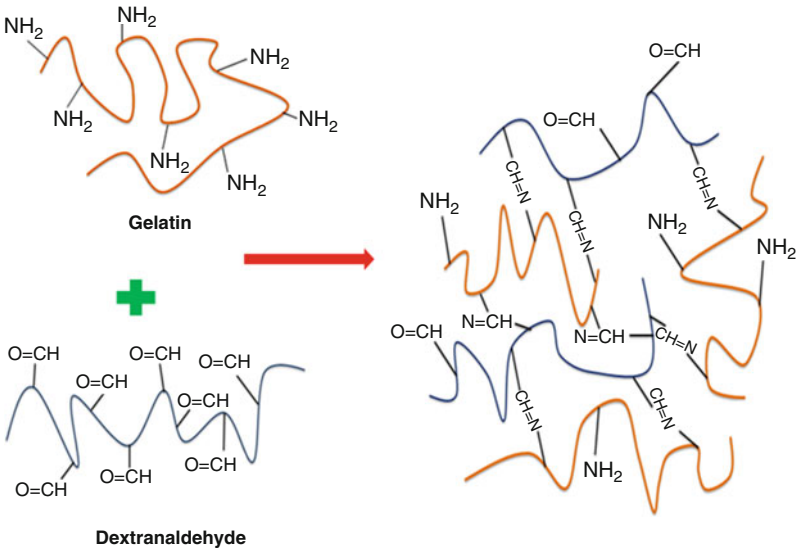

Fig. 6 Gelatin hydrogels crosslinked with partially oxidized dextrin [90]

was added to adjust the compressive modulus of the hydrogels. Huang et al. developed a CM-chitosan/gelatin hydrogels through radiation crosslinking approach which can be used as a promising wound healing material [97].

Besides using chitosan/gelatin hydrogels for wound healing material, sometimes natural phenolics are also added into the hydrogel system, and its application was observed as an antibacterial (antibacterial activity against *Pseudomonas aeruginosa* and *Staphylococcus aureus)* dressing for chronic wounded area. Under mild condition, the natural polyphenolic extract was collected from *H. virginiana which* was oxidized by laccase in a one-step process. Under the dual action, this laccase was also used to covalently crosslink chitosan and gelatin during hydrogel formation. Considering the synthesis technique, the natural phenolic compounds and tyrosine residue in proteins are oxidized by laccase which in turn converted into reactive quinones. This quinone further reacts with nucleophiles such as amino groups from chitosan and gelatin by 1,4-Michael addition or Schiff base formation [98].

Other than using natural product or chitosan derivative for the treatment of glaucoma, an injectable thermosensitive chitosan/gelatin/glycerol phosphate (C/G/GP) hydrogel as a sustained-release system of latanoprost was introduced by Cheng et al. [99].

In a very recent study conducted by Cheng et al., a thermosensitive hydrogel was fabricated by using chitosan and gelatin which was intended to be used in treating ischemic diseases through sustained release of adipose-derived stem cells. Among different techniques used for synthesizing chitosan/gelatin hydrogel, thermosensitive is considered advantageous since it does not need copolymerizing agents,

organic solvents, or an externally applied trigger for hydrogel formation. Considering chitosan-based thermosensitive hydrogel preparation, it needs only chitosan/glycerophosphate system. In this case the chitosan/gelatin hydrogel was fabricated by mixing chitosan-gelatin solution in glycerophosphate under controlled condition [100].

In Sect. 2.3.3 the formation of hydrogel through interpenetrating polymer network pathway was illustrated. The similar kind of technology was applied by Wang et al. who investigated the fabrication of in situ semi-IPN (interpenetrating polymer network) hydrogels by the free-radical polymerization and crosslinking reactions among chitosan, acrylic acid, gelatin, and N,N′-methylene-bis-acrylamide in an aqueous solution using gelatin as the interpenetrating component. Ammonium persulfate was used as an initiator of the free-radical polymerization. Deviating from the mainstream of biomedical and tissue engineering field, this hydrogel is solely applied in adsorbing the Cu^{2+} ion [101].

4.1.4 Gelatin-Polyvinyl Alcohol (PVA) Hydrogels

To fabricate chemical hydrogels from gelatin, condensation reaction is the second most popular way. Here a condensation reaction takes place between gelatin and other molecule, by eliminating a small molecule on being their combination. This kind of reaction was observed by Pal et al. during the formation of a hydrogel prepared from polyvinyl alcohol and gelatin. An esterification-condensation reaction occurred in presence of a catalyst (here, hydrochloric acid is used), between the two reacting sites of gelatin and polyvinyl alcohol (hydroxyl group of PVA with the carboxyl group of gelatin). The produced hydrogel membrane was proposed for biomedical application (e.g., contact lenses, artificial corneas, wound dressing, and coating for sutures, catheters, and electrode sensors) by the researchers [23]. In the field of tissue engineering, hydrogel from gelatin demands a chemical modification which could be achieved by covalent modification of proteins using crosslinkable functional groups and chemical grafting of synthetic polymers onto protein backbones. However, due to side chain disruption by chemical modification, protein degradation, denaturation, or loss of biological activity can be experienced. From this drawback, Lim et al. attempted to fabricate a gelatin-based hydrogel without performing any kind of modification to the protein molecule. As a result, a tyramine-functionalized poly (vinyl alcohol) (PVA) polymer (PVA-Tyr) was fabricated and finally turned into hydrogels with gelatin using a visible light-initiated crosslinking mechanism [102].

Most of the gelatin-based hydrogels are prepared for being used either in tissue engineering or biomedical implant field. However, Hui et al. explored a new hydrogel bead mainly prepared from PVA and gelatin through chemical crosslinking in the aqueous solution of saturated boric acid and $CaCl_2$ (curing agent) which is mainly applicable for adsorbing Pb(II). Besides PVA and gelatin, sodium alginate was added to provide the spherical skeleton for PVA hydrogel by curing. $CaCl_2$ reacted with carboxyl group present in the sodium alginate and gelatin, and as a result calcium ion can be induced into PVA crosslinking structure [103].

4.1.5 Gelatin–Alginate Hydrogels

Alginate is a linear anionic polysaccharide which is capable of forming ionic hydrogel in presence of divalent cation like calcium. Alginate has been extensively used in drug delivery and tissue engineering. However, non-biodegradability results from unmodified and photo-crosslinked alginate. Note that, photo-crosslinked alginate based hydrogel showed controlled mechanical properties [104, 105].

Wang et al. reported a hybrid hydrogel composed of alginate, gelatin, and nanocrystalline cellulose [106]. Here, gelatin provides the functional groups for chemical crosslinking. The novel hybrid hydrogels were synthesized through chemical bonding of alginate and gelatin. As well as ionic crosslinking of alginate with zinc ions and supramolecular interaction with nanocrystalline cellulose were also observed. The mechanical properties, crystallinity, and non-degradability of the hydrogel were improved by adding nanocrystalline cellulose; effective cell adhesion was obtained through gelatin molecule, whereas lower toxicity with controlled-ionic crosslinking was resulted from alginate and $ZnSO_4$. This injectable hydrogel was proved to be economically feasible for cell and growth factor delivery as well as healing bone defects [106].

Besides using pure alginate, some modified form of alginate was found to be observed in the field of biomedical and tissue engineering. In a study conducted by Yuan et al., sodium alginate and gelatin were used to synthesize double network hydrogels. A natural polysaccharide, sodium alginate, was modified by oxidizer to form aldehyde sodium alginate (ASA), and methacrylate groups were further grafted on the main chain of ASA forming aldehyde methacrylate sodium alginate. The second element gelatin was modified with ethylenediamine (ED) forming amino gelatin which can graft more amino groups. When aldehyde methacrylate sodium alginate and amino gelatin aqueous solutions were mixed, the Schiff base reaction occurred quickly to form the primary network between aldehyde groups in aldehyde methacrylate sodium alginate and amino groups in amino gelatin. After that to produce the secondary network, a 365 nm ultraviolet (UV) light was applied for initiating the radical reaction of methacrylate groups in aldehyde methacrylate sodium alginate. This double network hydrogels may have great potential application in the field of therapeutic materials and regenerative medicines [107].

In a recent study, Balakrishnan et al. reported the use of oxidized alginate in forming hydrogel with gelatin. Rather than using toxic crosslinking agents, the authors preferred to use self-crosslinking technique [105]. Thus periodate-oxidized alginate and gelatin undergo self-crosslinking in the presence of borax, to form in situ gelling hydrogels. The hydrogelation happens between periodate-oxidized alginate and ϵ-amino groups of lysine residues of gelatin through en route of borate-diol complexation followed by Schiff reaction. This self-crosslinked hydrogel may be predicted to be a promising agent for neo-cartilage formation as well as in treating osteoarthritis [105].

4.1.6 Gelatin–Carbon Nanotube Hydrogels

The addition of carbon nanotube imparts good electrical conductivity to the gelatin-based hydrogel [108]. In general, a hybrid gelatin hydrogel with carbon nanotubes

was prepared by physically mixing the ingredients [25]. A modified grafting technique and emulsion polymerization method are involved in presence of sodium methacrylate and N,-ethylenebisacrylamide to fabricate the hybrid hydrogel from gelatin and multiwalled carbon nanotubes. In addition, different amounts of nanotubes were covalently incorporated into the polymeric hydrogel network in order to determine the percentage bestowing the maximum electric sensitivity to the hybrid hydrogel composite microspheres. A modified grafting from approach was used which involves a direct one step polymerization of the unmodified multiwalled carbon nanotubes. The prepared hydrogel was mentioned to be used as a drug delivery microsphere which can turn on the electro-responsive release of Diclofenac sodium salt investigated by Spizirri et al. [109].

In a different study, multiwalled carbon nanotubes (MWNTs)/gelatin composites were synthesized by dispersion of MWNTs through ultrasonication in an aqueous medium. An anionic surfactant, e.g., sodium dodecyl sulfate, was used for the hydrogel fabrication [108]. Similarly within the gelatin hydrogels, functionalized single-walled carbon nanotube has been incorporated and dispersed to make hybrid hydrogel better suited in terms of stability, elasticity, and conductivity compared to native gelatin-based gel [110].

It is also possible to fabricate the hybrid hydrogel with carbon nanotube by using methacrylate gelatin (GelMA). This type of study was conducted by Shin et al. where the methacrylate gel coating was applied on the carbon nanotube (CNT). GelMA is photopatternable that allows the easy fabrication of microscale structure. The coating is possible due to the hydrophobic interaction between the polypeptide chains of the GelMA and the sidewalls of the nanotubes. The authors indicated the possible use of this CNT reinforced methacrylate gelatin hydrogel in fabricating complex 3D biomimetic tissue-like structures or can be used in in-vitro cell studies [111].

Other than these much classified sections of gelatin-based hydrogels, some hydrogels can be fabricated by using renowned crosslinker or crosslinking techniques. Some of them are stated below:

The most common crosslinking agent used for gelatin-based hydrogels is glutaraldehyde. In a study of Tabata et al., fibroblast growth factor was incorporated both in acidic and basic gelatin-based hydrogels, differing in isoelectric point. However, both of the gelatins use glutaraldehyde as the crosslinking agent, and a chemical crosslinking reaction takes place between gelatin and glutaraldehyde [112].

From the data obtained by the researchers, it is well understood that aldehyde is considered as a good crosslinker for covalent crosslinking of gelatin without chemical modification. Howsoever, aldehyde is avoided for simultaneous cell encapsulation application due to its immunogenicity, cytotoxicity, and inflammatory effects of their degradation products [113]. In a replacement of aldehyde, genipin, a natural crosslinking agent, is used, which is deliberated less cytotoxic compared with aldehydes. But it must be used at a low dose when the hydrogel is used to encapsulate cells [114]. Over and above, major disadvantages of direct crosslinking methods (without prior modification of gelatin) include poor control over the crosslinking density and the resulting stiffness of the hydrogel. For these reasons,

using functionalized gelatin has become a favorable way over the direct crosslinking of gelatin [26].

Compared with direct crosslinking techniques, introduction of functional groups to the gelatin backbone is a crosslinking strategy, with a high degree of control over hydrogel design and properties. Two frequently used techniques for hydrogels preparation after functionalization are (photo)-radical-initiating systems and enzymatic crosslinking of functionalized gelatin. Photoinitiation provides good temporal and spatial control on the crosslinking process over direct crosslinking techniques, which is essential for constructing an architecturally complex tissue analog. For photoinitiation, both ultraviolet light (UV) and visible light (VIS) are used [26]. However, enzymatic crosslinking of gelatin under physiological conditions by means of transglutaminases or tyrosinases ensures a better cell friendly approach [115].

4.2 Properties (Physical and Chemical)

Native gelatin has found to show low level of immunogenicity and cytotoxicity, biodegradability, clotting property, etc. Specifically, scientists have explored modification of the gelatin backbone with PEG-dialdehyde and/or ethylene-diamine-tetraacetic dianhydride (EDTAD) to alter the physicochemical properties of the gelatin and to affect the subsequent release, degradation, and solubility of model drugs from and within the hydrogel. Modification of gelatin with EDTAD introduces polyanionic molecules into the gelatin chain, increasing the hydrophilicity of the gelatin backbone with the addition of charged groups and thereby potentially improving the swelling capability of the resulting hydrogel. Additionally, modulation of the crosslinking modality (i.e., percent glutaraldehyde or self-crosslinking via exposure to dry heat) of unmodified and modified gelatin are introduced to affect the solubility and density of the resulting matrix, which contribute to the swelling/degradation and the release mechanism of therapeutic agents [24].

Earlier it was discussed that the gelatin gels are nearly unstable at body temperature because of their low melting point. So, it is necessary to stabilize the gelatin gels before they can be used for wound healing purposes in contact with the body. This is usually done by crosslinking between the protein chains by treating the gelatin with either formaldehyde or glutaraldehyde as crosslinkers. Alternatively, this can be achieved by crosslinking of gelatin with polyaldehydes produced by partial oxidation of polysaccharides such as dextran. Alone or in combination, gelatin and dextran are widely used for drug delivery systems [93].

Because of the acidic property of gelatin-based hydrogels, sometimes they are used for storing the basic fibroblast growth factor (bFGF). bFGF is known to be stored in the body through ionic complexation with acidic polysaccharides of the extracellular matrix such as heparan sulfate and heparin. This poly-ion complexation property of gelatin protects bFGF from in-vivo denaturation and enzymatic degradation [112].

Some recent studies have shown a possible way to fabricate recombinant gelatin which exhibited well-defined sequence, molecular weight, and isoelectric point compared to nonrecombinant gelatin. This property also enables the gelatin to become crosslinked with methacrylate residue by radical polymerization. Particularly, compared to other hydrogels, methacrylated recombinant gelatin-based hydrogels are better suited for the protein delivery [92].

4.3 Applications in Variegated Fields

4.3.1 Tissue Engineering

Tissue engineering is a modern technique to treat the imperfection due to injury, disease, and failure both in the tissue and the body. A peroxidase-catalyzed enzymatic crosslinking of the gelatin chain results to a gel that does not melt at 37 °C. In this case the gelatin was modified by incorporating a phenolic hydroxyl group. The control in phenolic group imparts an effect on gelation time, mechanical properties, and proteolytic degradability. The application of this kind of gel was found in both tissue engineering and drug delivery fields. In addition, in case of practical application of this gel, researchers have injected a mixture of produced gel (gelatin-phenolic hydroxyl), horseradish peroxidase, and H_2O_2 which have successfully gelled at the injected site in-vivo and remained intact for 1 week without inducing necrosis in the surrounding tissues [92]. However, various types of enzyme enable the formation of hydrogels from gelatin through many different ways (Table 1).

In the field of tissue engineering, a hydrogel can be composed of mainly gelatin methacrylamide and polyethylene glycol (PEG). Both the crosslinking reaction of PEG and the incorporation of gelatin methacrylamide were formed by two distinct types of coupling reaction. This kind of hydrogels showed enhanced mechanical integrity and cytocompatibility and thus is accepted for tissue engineering scaffold application [119].

The following table (Table 2) has enlisted some of the recent developments in the field of tissue engineering by gelatin-based hydrogels.

4.3.2 Drug Carrying Vehicles

Gelatin, the biological macromolecule, due to its biodegradable, biocompatible, non-antigenicity, and low cost with easy availability, it is considered as a versatile drug/vaccine delivery carrier in pharmaceutical field. The main reason behind this drug

Table 1 List of enzymes helping in the formation of gelatin-based hydrogels

Sl. No.	Material	Enzyme	Application	Reference
1.	Gelatin	Microbial transglutaminase	Tissue engineering scaffolds	[116, 117]
2.	Gelatin-chitosan conjugates	Tyrosinase	Tissue glue Wound dressings	[118]

Table 2 Gelatin-based hydrogels in tissue engineering application

Sl. No.	Hydrogel fabrication main materials	Purpose	Reference
1.	Gelatin-methacrylate	Bone replacement materials	[120]
2.	Gelatin-methacrylamide û Hyaluronic acid methacrylate	Tissue engineering	[121]
3.	Gelatin/hyaluronan	Treatment of brain injury	[122]
4.	Collagen-chitosan-hydroxyapatite û Gelatin	Biodegradable scaffold	[123]
5.	Gelatin/alginate/fibrinogen	Hybrid cell/hydrogel construct	[124]
6.	Gelatin, sodium alginate	Tissue engineering	[125]
7.	Gelatin/chitosan and type I collagen	Tissue engineering scaffolds	[126]

attachment is the primary structure of gelatin that offers chemical modification and covalent drug attachment with gelatin. This kind of drug attachment can be done either within the matrix of the particles or on the particle surface only [127]. Moreover, gelatin-based hydrogels are considered to boost up the drug attachment/loading due to its high porosity that can easily be adjusted by controlling the affinity to water and the density of crosslinks in their matrix. The advantages offered by hydrogels for drug delivery applications include the possibility for sustained release [127]. The hydrogel carrying drug can be applied to various tissues of the human body, e.g., ocular, nasal, oral cavity, stomach, small intestine, colon, rectum, transdermal, etc. [128].

An injectable physically crosslinked gel-like structure was fabricated from several blends of natural polymers. One of the blends is gelatin-agar combination. The other similar types of blends are starch-carboxymethyl cellulose, hyaluronic acid-methylcellulose, etc. Due to the absence of chemical crosslinker and as the formulations are resembled to extracellular matrix polymers, gelatin-agar hydrogel exhibits excellent biocompatibility. However, hydrogen-bonded networks can dilute and disperse over a few hours in-vivo due to influx of water. This restricts the use of hydrogel to relatively short-acting drug release systems unless some other form of crosslinking is also used [129].

In a different study, a quick gel-forming hydrogel was fabricated from oxidized konjac glucomannan and gelatin. Oxidized konjac glucomannan was added as a crosslinker. The composite hydrogels were sensitive to the pH value of the medium. The results of in-vitro drug (ketoprofen) release experiments showed that all the hydrogels showed sustained release properties and the dependence of release rate on the equilibrium swelling ratio of hydrogels and pH value of medium [130].

Instead of using physical crosslinker, chemical crosslinker can also be used to fabricate gelatin-based hydrogels. An example of this type is the fabrication of magnetic hydrogels by chemically crosslinking of gelatin hydrogels and Fe_3O_4 nanoparticles through genipin (GP) as crosslinking agent. Smart magnetic hydrogels based on gelatin-ferrite composites were investigated and can be applied for the development of a new magnetically induced drug delivery system. Furthermore, the drug release profile of the resulting hydrogels is controllable by switching “on” or “off” mode of a given magnetic field [131].

Table 3 Gelatin-based hydrogels as a drug carrying media

Sl. No.	Hydrogel fabrication main materials	Purpose	Reference
1.	Gelatin/monomethoxy poly(ethylene glycol)-poly(D,L-lactide)	Antibacterial drug delivery	[133]
2.	Gelatin-poly(ethylene Oxide) semi-interpenetrating polymer network	Oral drug delivery	[134]

A plant-originated polysaccharide (κ-carrageenan) has been used to prepare one component and blend hydrogels, with two natural polymers, agar and gelatin, for the release of a drug theophylline. In the mixed system, the additional crosslinking between the chains of the different molecules slowed down the diffusion rate of the guest drug molecule through matrix [132]. Some other drug delivering hydrogel matrices are listed below in Table 3.

4.3.3 Wound Dressing Agent

Modern dressings are designed to facilitate wound healing rather than just to cover it. A novel membrane of the hydrogel was prepared by Kunal et al. from gelatin and polyvinyl alcohol. The prepared hydrogel was observed to show hemocompatibility and moisture retentive property that enabled its possible use in moist wound care. To keep the wounded area moist is really very helpful as it speeds the healing process by absorbing exudates while maintaining the products of tissue repair, including lysosomes and growth factor in contact with the wounded area [135]. Blood is the pathway to work for most of the drugs. Adrenochrome is a blood coagulating agent which has been added to a hydrogel comprising of gelatin and polyvinyl alcohol along with some other materials. This hydrogel is used in wound healing function in different forms like patch, gel, ointment, etc. The gelatin with adrenochrome in hydrogel has a synergistic effect in wound healing [136].

A wound dressing hydrogel material was described by Balakrishnan et al. that is capable of treating the wound within 10 days without any side effect. This hydrogel was fabricated in situ from gelatin and oxidized alginate containing dibutyryl cyclic adenosine monophosphate [136].

Another gelatin-based hydrogel pad was described by Rattanaruengsrikul et al. This pad was fabricated from gelatin and $AgNO_3$ which turned into nano silver particle upon mechanical stirring in presence of acetic acid. However, for crosslinking purpose glutaraldehyde was added into the mixture of $AgNO_3$ and gelatin. This pad was found effective against both the gram-positive (*Staphylococcus aureus*) and gram-negative (*Escherichia coli*) bacteria and therefore suggested to be used as an antibacterial wound dressing pad [137].

A specialized hydrogel dressing for patients with burn was fabricated from gelatin, chitosan, and honey (Fig. 7). Chitosan has been widely used for wound dressing in the form of hydrogel. In fact, honey has been commercially used for

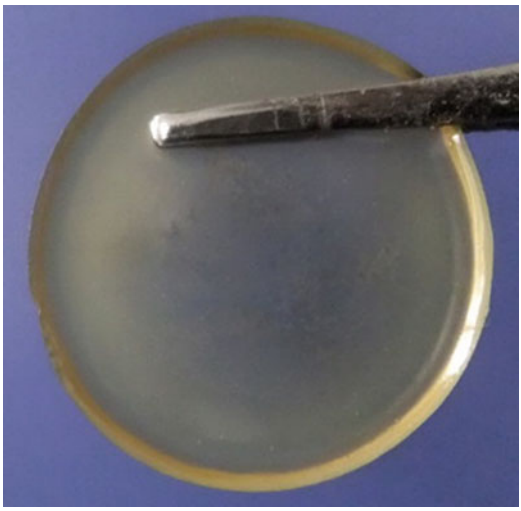

Fig. 7 Photographic appearance of the hydrogel sheet composed of gelatin, honey, and chitosan [138]. (Copyright © 2017, Elsevier)

wound dressings due to its suitability for all stages of wound healing. Gelatin is a biocompatible protein with excellent water absorbing power. Especially for these reasons, the three materials were chosen for preparing hydrogel dressing sheets, which showed better performance in wound healing better than typical antibiotics ointment (MEBO® ointment, Shantou MEBO Pharmaceuticals Co., Ltd., Guangdong, China) or without any treatment. The sheet took 12 days to treat the wounded area (Fig. 8). In addition, it had powerful antibacterial efficacy to *S. aureus* and *E. coli* and significantly promoted burns healing. Moreover, upon swelling in water from 40% to 130%, the prepared hydrogel was discovered with microporous cross-section from smoother one. Further increase in water content (200%) tends to give a collapsed surface with increase in pore size compared to hydrogel containing 130% water. However, the opposite phenomenon was espied in case of pore numbers. More pores were observed in case of hydrogel containing 130% water compared to hydrogel with 200% water (Fig. 9) [138].

Besides chitosan/gelatin hydrogel, it is possible to fabricate pectin/gelatin hydrogel, which is available in the form of membrane and can be used as a wound dressing material. This material was developed by Mishra et al. The hydrogel membrane showed enhanced thermal stability, tensile strengths, and elongation at break up to a certain percentage of gelatin in the hydrogel. An intermolecular interaction was observed between the two naturally occurring polymers that also showed better moisture retentive property which enabled this membrane to be applied as moist wound care element [139].

A very recent paper deals with a new composite material. As an antitumor agent, gelatin-based hydrogel is a promising candidate that is capable to restore water as well as desired drug in proper amount with appropriate way to release in the body stream. Such kind of hydrogel was prepared by Konishi et al. by chemical

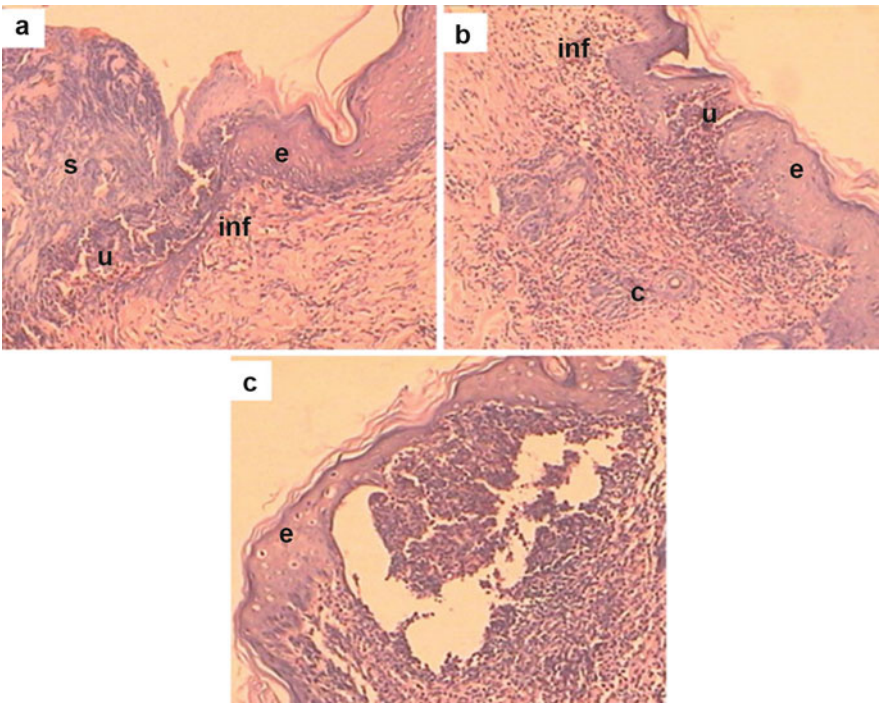

Fig. 8 Photomicrographs of burn wound tissues at day 12 post-burned: (**a**) untreated wound, (**b**) MEBO treated wound, (**c**) gelatin-, honey-, and chitosan-based hydrogel-treated wound, *s* scab, *u* ulcer, *inf* inflammatory cells, *c* cyst, *e* epidermis (100×) [138]. (Copyright © 2017, Elsevier)

crosslinking of gelatin with different concentrations of glutaraldehyde containing "cisplatin" as the drug with control release.

4.3.4 Protein Releasing Media

A crosslinked hydrophilic polymer is considered as a media for absorbing large amount of compatible penetrant (e.g., water). This polymer gets swelled, thus forming a gel and called as hydrogel. During the swelling process if there exists any solute, the material releases that solute to the environment. In many cases the solute is a drug material. This property of hydrogel material has been practiced for delivering drug for more than a decade. However, it is now trying to use the hydrogel material to deliver protein due to its ability to release drugs at a zero order rate and to target proteins to specific sites, such as the upper small intestine, which extends their biological activity [140]. Gelatin is a well-known polymer to fabricate hydrogel in many ways with or without the presence of a supporting material other than crosslinker. Some recent developments in the protein releasing field by gelatin-based hydrogel have inspired the researchers to explore more and more ways of its fabrication, modification, and application in the protein releasing field.

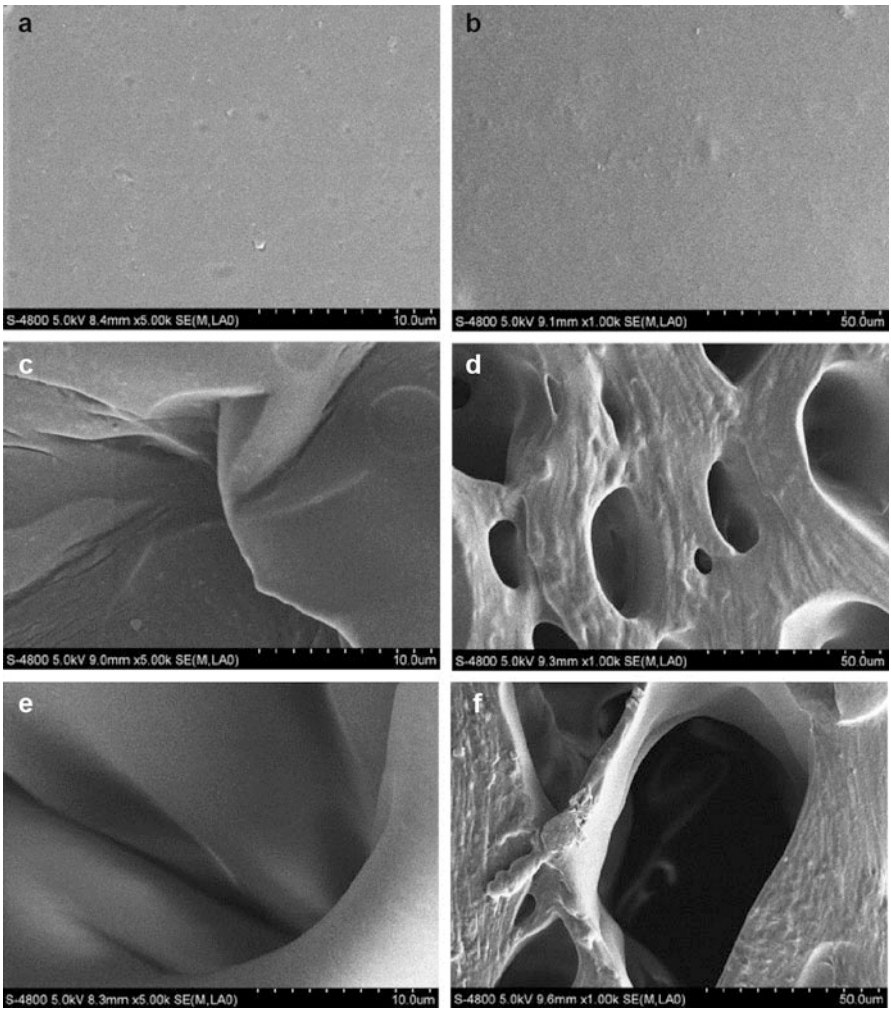

Fig. 9 SEM images of the lyophilized hydrogel sheet HS with different water content. Surface morphology of HS with 40% water (**a**), 130% water (**c**), 200% water (**e**), and (**b**), (**d**), and (**f**) the corresponding cross-section morphology [138]. (Copyright © 2017, Elsevier)

Various antibacterial proteins are discovered by the researchers to apply in various antibacterial purposes through incorporating with hydrogel originated from gelatin. A study conducted by Kujipers et al. describes that during the cardiac valve replacement a serious complication was observed due to the infection caused by the adherence of bacteria to the prosthetic valve or to tissue at the site of implantation. The release of an antibacterial protein through crosslinked gelatin hydrogel can reduce or diminish the possibility of infection. In a release system, the antibacterial proteins incorporated in the Dacron sewing ring of the prosthetic heart valve would

cut down the incidence of prosthetic valve implantation complication due to the infection. This hydrogel was tested for uptake and in-vitro release of lysozyme, a small antibacterial cationic protein [141].

Using the same incorporation base (i.e., Dacron) but different fabrication materials other than gelatin, it is also possible to prepare an antibacterial protein releasing hydrogel. A chemically crosslinked gelatin-chondroitin sulfate (ChS) hydrogel was prepared, impregnated in Dacron, and crosslinked with a water-soluble carbodiimide (EDC) and *N*-hydroxysuccinimide. This hydrogel is capable of releasing lysozyme and recombinant thrombocidin. As a part of the practical application of this hydrogel, it is implanted in the subcutaneous pockets in rats which showed a mild tissue reaction and almost complete degradation within 18 weeks of implantation [142].

Besides antibacterial protein bone morphogenetic proteins can also be loaded in the gelatin-based hydrogel system. One of these studies was conducted by Chen et al. They investigated the formation of bone morphogenetic proteins by radical crosslinking and low dose ϒ-irradiation from glycidyl methacrylated dextran and gelatin. The researchers also found that BMP release from microsphere temperature-sensitive hydrogel compounds could be accordingly controlled and the release period could be varied from 18 to more than 28 days with biodegradation quality [143].

In a different study of protein release, amino acid modified gelatin hydrogels slow down the release of lysozyme and trypsin inhibitor protein. To an extent the release rate is directly proportional to the strength of the charge interactions between the amino acid chain and the entrapped proteins [92]. Besides using pure, non-modified gelatin recombinant, gelatin can also be used in fabrication of hydrogel material. For hydrogel fabrication, recombinant gelatin is preferred because of its well-defined molecular weights, amino acid sequences, and isoelectric points. Sutter et al. used this kind of recombinant gelatin modified with methacrylate residues for chemical crosslinking and gel formation which is used for sustained release of the protein. For experimental purpose, release of the incorporated model proteins lysozyme and trypsin inhibitor occurred by diffusion. Recombinant gelatin derived hydrogels were enzymatically degradable by human matrix metalloproteinase which indicates in-vivo biodegradability [92].

So far we discussed the release of a single protein by gelatin-based hydrogel. However, a significant one is the release of multiple proteins through combination of their mechanism and rates of the hydrogel materials. An example of this class is the fabrication of hydrogel from glycidyl methacrylate and polyethylene glycol with gelatin [144]. The growth factor(s) (mainly protein) can be attached to the hydrogel matrix in many ways. Then the growth factors are delivered to the cell that results in tissue regeneration phenomena. A general representation of this process is shown in Fig. 10 [144].

It is also possible to fabricate two protein based hydrogel. A study conducted by Gil et al. suggested that a thermo responsive gel can be prepared by blending gelatin and silk fibroin which was stabilized at 37 °C by the presence of crystals of silk fibroin. The swelling profile of this hydrogel material below and above the temperature allows it to release protein from the matrices. The gel showed a higher swelling

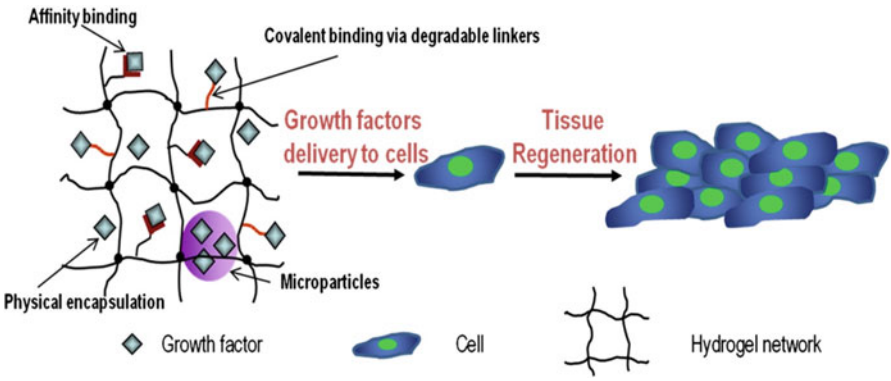

Fig. 10 Hydrogel for protein delivery and tissue regeneration [144]. (Copyright © 2017, Elsevier)

at physiological temperatures as compared to 20 °C. However, a higher mass loss was also observed due to dissolution and release of gelatin [145].

4.3.5 Extracellular Matrix and Growth Factor Release

A new type of covalent synthetic extracellular matrix (ECM) was developed through a new disulfide crosslinking method. For preparing ECM, blended hyaluronan (HA)-gelatin hydrogels are formed initially. Both the HA and gelatin were chemically modified using 3,3′-dithiobis(propionic hydrazide) (DTP). After reduction with dithiothreitol (DTT), the thiol derivatives of HA and gelatin were obtained. Both the modified HA and gelatin were blended in different concentration and prepared in 1% NaCl solution. The mixture was crosslinked by disulfide bond in air, and a second crosslinking was performed in presence of hydrogen peroxide. The degradation of the hydrogels by the enzymes was governed by the ratio of modified HA and gelatin and the type of enzyme responsible for degradation [146].

For control releasing of a biologically active growth factors, Yamamoto et al. developed biodegradable hydrogels carrier through glutaraldehyde crosslinking of gelatin with isoelectric points (IEP) of 5.0 and 9.0, i.e., "acidic" and "basic" gelatins, respectively. Basic fibroblast growth factor (bFGF) and transforming growth factor-β 1 (TGF-β1) are basic in nature and that were found well sorbed with time to the acidic gelatin hydrogel, while less sorption was observed for the basic gelatin hydrogel. Nevertheless, bone morphogenetic protein-2 (BMP-2) and vascular endothelial growth factor (VEGF) were sorbed to the acidic gelatin hydrogel to a smaller extent than the two other growth factors though their IEPs are higher than 7.0. Both in-vivo and in-vitro analyses indicate that the growth factor immobilized to the acidic gelatin hydrogel through ionic interaction was released in-vivo as a result of hydrogel degradation [147].

In another study the release of fibroblast growth factor was found to be more efficient when impregnated in a hydrogel compared to free growth factor. This is possible due to the in-vivo degradation of the hydrogel. The hydrogel material was fabricated by crosslinking of acidic gelatin with the isoelectric point of 4.9. It was

concluded that, the fibroblast growth factor impregnated in a hydrogel leads to more efficient induction of neovascularization and tissue granulation than free fibroblast growth factor without impregnation in the hydrogel [148]. In a different investigation, the release of growth factor by thiolated gelatin/thiolated hyaluronic acid/polyethylene glycol diacrylate-based networks was described by Peattie et al. [149].

4.3.6 Bioadhesive

The major goal of bioadhesive controlled drug delivery is to enhance the drug absorption process in a site specific manner through localizing a delivery device within the body. Hydrogel materials from various sources can be used as a bioadhesive agent. Other than direct biomedical uses, gelatin-based hydrogels can be used as biological glue or bioadhesive materials.

A hydrogel fabricated from gelatin-poly (γ-glutamic acid) could be applied as soft tissue mixed adhesives. For a faster mixed adhesive fabrication, a crosslinker is necessary. The molecular weight of gelatin and poly (γ-glutamic acid) increases the bonding strength but lessens the time required for gelation. The investigation of the mixed adhesives result no cytotoxicity and no inflammatory response [150].

A supramolecular hydrogel macromer was fabricated from aromatic residue of gelatin and photo-crosslinkable acrylated β-cyclodextrin (Ac-β-CD) monomers. The subsequent crosslinking of the macromers produces highly resilient supramolecular gelatin hydrogels that are solely crosslinked by the weak host-guest interactions between the gelatinous aromatic residues and β-cyclodextrin (β-CD). This host-guest supramolecular macromer (HGM) was used to fabricate the final mechanically robust gelatin-based hydrogel (Fig. 11). The excess β-CDs in the hydrogels enable the tissue adhesion and enhance the loading and sustained delivery of hydrophobic drugs. Besides tissue regeneration application, the hydrogels are also considered as a bioadhesive and are able to retain and release hydrophobic drugs, thereby enabling the delivery and long-term release of drugs at the targeted locations. Moreover, it was also observed that the prepared hydrogel is favorable to glue two fractured femoral swine bones together. The adhesion property of the HGM hydrogel was compared to the adhesive power of methacrylated gelatin macromer-based hydrogel, and the HGM hydrogel showed better adhesion power in case of swine femoral bone even after the addition of 100 g weight in excess to the lower part of the bone [151].

The use of different crosslinker materials has a noticeable effect on the properties of the hydrogel material, e.g., adhesion power, gel formation time, cytotoxicity, etc. Gelatin was crosslinked with different materials, and their properties as a bioadhesive were evaluated in a study conducted by Wen Sung et al. to select the right adhesive for a particular application. Gelatin and resorcinol were crosslinked with formaldehyde (GRF glue), glutaraldehyde (GRG glue) and epoxy (GRE glue), carbodiimide (GAC glue), and genipin (GG glue). It was found that GRE, GRF, and GRG are more cytotoxic compared to GAC and GG. However, GRF and GRG showed maximum adhesion in minimum time and therefore suggested to be used

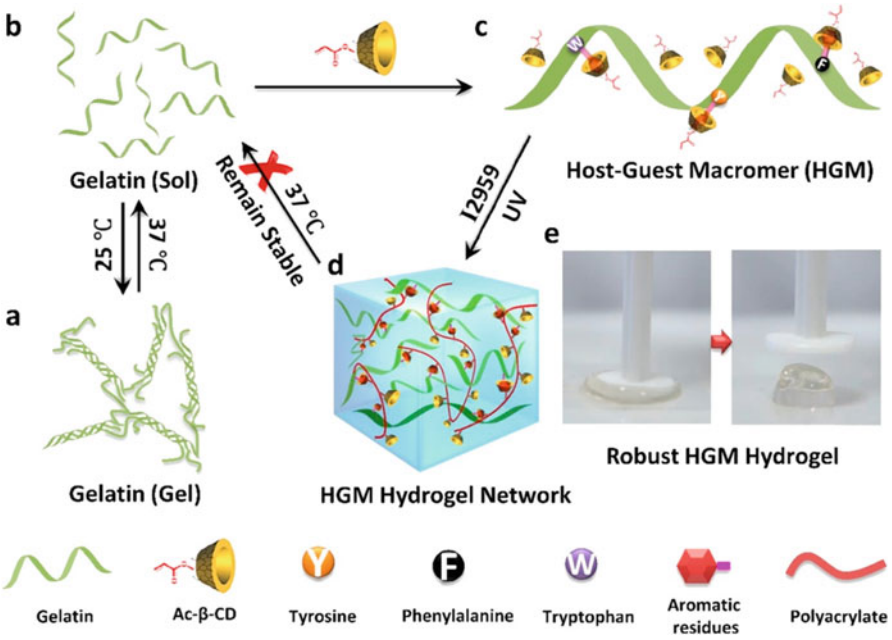

Fig. 11 (**a**) Pure gelatin solutions form hydrogel below 30 °C. (**b**) The gelatin hydrogels dissolve at 37 °C. (**c**) Formation of host-guest macromere (HGM) through complexation between the free diffusing monofunctional Ac-β-CDs (with one single acrylate group per β-CD) and the aromatic residues of gelatin. (**d**) The acrylate groups in the gelatin HGM leads to the formation of the HGM supramolecular hydrogels by UV-initiated radical polymerization, which are stable at 37 °C. (**e**) The HGM hydrogels can withstand cyclic excessive compression that represent its excellent compressibility [151]. (Copyright © 2017, Elsevier)

when a rapid and tight bonding is required. GAC and GG exhibited comparable adhesion power, while GRE showed no binding strength [43].

The practical application of some of the hydrogels stated above was described by Wen Sung et al. in another study. It was suggested that the cytotoxicity of the GRF glue can be reduced by changing the pathway of crosslinking operation. As a part of the change in the pathway, an alternative crosslinker water soluble carbodiimide or genipin had been introduced which formed GAC glue and GG glue. These GAC and GG were applied to close skin wound lesions in a rat model.

A very common crosslinking agent is polyacrylic acid. A gelatin-based hydrogel was fabricated by Ghavamzadeh et al. by using polyacrylic acid. This hydrogel was applied in-vitro as a bioadhesive material for soft tissues. To crosslink the mixture of gelatin and polyacrylic acid (PAA), water-soluble carbodiimide (WSC) was used. The cured hydrogel showed sufficient adhesion to mouse skin with a higher bonding strength compared to fibrin glue [152].

However, most of the gelatin-based hydrogels are focused on mainly biomedical and tissue engineering application; some gelatin-derived hydrogels are fabricated for adsorbing metals like lead and copper [103]. Besides these, sometimes carbon

nanotubes are found to be incorporated in the gelatin-based hydrogel forming a hybrid suitable for drug delivery, encapsulation with tuned mechanical strength and biocompatibility [109, 111].

5 Conclusions

Hydrogel based networks have been considered as important tools to meet the needs of different applications because of their physical and chemical characteristics and technical feasibility of utilization. Although, during the last two decades, natural hydrogels were gradually replaced by synthetic hydrogels due to long service life, high capacity of water absorption, and high gel strength of the latter, still natural polymers are the key components of most of the natural and synthetic hydrogels due to their numerous availabilities. Researchers, over the years, have developed a well variety of gelatin and modified gelatin-based hydrogels. Because of their well-controllable network, they become attractive materials for numerous fields of application like tissue engineering, drug delivery, wound dressing, protein releasing media, growth factor matrix, etc. A wide range of smart gels, combining gelatin with other natural/synthetic polymers, with different mechanical properties and potential applications in different fields can be produced through the correct control of the different experimental parameters and the addition of well-compatible crosslinker. We hope that the current rate of advancements in this field will yield the next generation efficient materials with availability for different biomedical applications.

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Collagen-Based Hydrogels and Their Applications for Tissue Engineering and Regenerative Medicine

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Abstract

A promising solution for soft tissue regeneration is tissue engineering, a multidisciplinary field of research which involves the use of biomaterials, growth factors, and stem cells in order to repair, replace, or regenerate tissues and organs damaged by injury or disease. The success of tissue engineering (TE) depends on the composition and microstructure of the used scaffolds. Ideally, scaffolds have to be similar to natural tissues. Collagen is the major component of the extracellular matrix of most soft tissues. The interactions between collagen and cells are vital in the wound healing process and in adult tissue remodeling, collagen being able to support differentiation and maintenance of cellular phenotype. As a natural molecule, collagen possesses the major advantage of being biodegradable, biocompatible, easily available, and highly versatile and presents low antigenicity. This chapter aims to present an overview on the structure, properties, and biomedical applications of collagen hydrogels. Moreover, it introduces the reader to the latest research in the field of tissue engineering related to collagen. It also displays the results we obtained as a joint bioengineering group on collagen hydrogels designed for soft (ATE) or cartilage tissue engineering (CTE) applications: type I collagen hydrogels improved with either silk sericin (CollSS) or with pro-chondrogenic factors – hyaluronic acid and chondroitin sulfate (CollSSHACS). Results indicated in both cases the positive influence of sericin on the interaction between cells and the surface of the hydrogels. In the absence of HA and CS, specific chondrogenic inducers, CollSS hydrogel is adapted for soft tissue reconstruction, whether the addition of HA and CS transforms CollSSHACS into a suitable hydrogel formula for semihard tissue repair via modern strategies in tissue engineering and regenerative medicine.

Keywords

Collagen hydrogels · Biomaterial · Regenerative medicine · Tissue engineering · Sericin · Hyaluronic acid · Chondroitin sulfate

1 Introduction

Hydrogels are three-dimensional (3D) polymer networks that are able to maintain a large amount of water and biological fluids, whose physical and chemical crosslinks between polymer chains keep their structural integrity [1, 2]. The polymer chains can be natural, synthetic, or hybrid [3]. The natural polymers like collagen, chitosan, elastin, alginates, hyaluronic acid, pullulan, and fibrin have been processed from living organisms. Having a similar structure with the extracellular matrix, natural polymers possess good biocompatibility properties with low cytotoxicity. However, because of processing/extraction, they are not preserving mechanical properties [4]. The synthetic polymers generally used in hydrogels preparation are poly(ethylene glycol) (PEG), poly(acrylamide) (PAM), poly(vinyl alcohol) (PVA),

polyethylene oxide (PEO), poly(acrylic acid) (PAA), and poly(propylene fumarate-co-ethylene glycol) P(PF-co-EG) [5, 6], which possess controllable chemical and mechanical features but less biocompatibility properties. In the last 20 years, hybrid hydrogels consisting in both natural and synthetic polymers have been developed in order to provide a better quality of life, mechanical resistance, and water absorption capacity [3].

The applications of hydrogels are multiple and in different research areas such as pharmaceuticals, biomedical implants, drug delivery, tissue engineering, and regenerative medicine [1]. The hydrogels were found to be ideal for clinical applications, in healing of wounds and burns and even necrotic tissue due to their ability to transfer vapor and oxygen resulting from their high-water content applied to the wound site [5].

Due to tissue-mimicking characteristics, the most recent research recommended the use of hydrogels as scaffolds to provide a biomimetic 3D microenvironment for the growth of cells [4].

Regenerative medicine is an emerging multidisciplinary field of research which involves the use of biomaterials, growth factors, and stem cells in order to regenerate, repair, or replace tissues and organs damaged by injury or disease. Currently, tissue engineering applications are focused toward the use of implantable biohybrids consisting of scaffolds combined with stem or precursor cells and appropriate inducers, as a regeneration strategy.

The objective of this chapter is to describe the structure, properties, and main applications of collagen hydrogels for practical applications in Biology and Medicine and to present our main findings in this field of research.

2 Collagen-Based Hydrogels: Overview

Collagen is the main natural protein of most soft, lax, semirigid, and rigid connective tissues (skin, bones, tendon, basal membranes, etc.), providing mainly structural integrity for tissues [7]. Collagen is found in proportion of 80% at skin level, reported to all dermal dry substances [8, 9].

Collagen is a polymer which is characterized by high hydrophilicity, variable ionic character, and diverse functionality and can be involved in a large number of interaction systems with other micro- and macromolecular components [10, 11].

Collagen is an amphoteric macromolecule with rigid triple helix conformation, containing both polar groups and hydrophobic portions derived from hydrophobic amino acids. Consequently, at pH values outside the isoelectric range, between the molecules, fibrils, and chain fragments of the non-denatured type I fibrillar collagen, all types of intramolecular electrostatic, dipole-dipole, hydrogen and hydrophobic bonds can be established in the aqueous medium. This may be the reason why aqueous systems of this type of collagen become gels at low concentrations compared to denatured collagen (gelatin or collagen hydrolysates), which have the molecules in the form of statistical coils.

The most used collagen extracts which are basic resources for obtaining medical biomaterials are type I collagen gels and solutions. A gel is defined as a system with intermediate properties between a fluid and a solid. Thus, a gel can be a less viscous fluid or a very viscous solid. At isoelectric pH, the fibers and fibrils are separated from the collagen gel, making it dispersible. Collagen gels and solutions are polydispersed colloidal systems, despite tropocollagen solutions which are monodispersed, containing only molecules with triple helix conformation.

According to our experience, type I fibrillar collagen extracted from the calf hide by acidic and basic treatments at temperatures between 18 °C and 25 °C, with an average molecular weight of $3.1–3.3.10^5$ g/mol, consists of native collagen molecules, fibrils, and fragments of single chains.

The rheological study of non-denatured type I fibrillar collagen gels at pHs outside the isoelectric range, acid (2.5–4), neutral (7.0), and alkaline (8.0), showed that they have pseudoplastic behavior, more obvious at higher concentrations. Viscosity at zero shear rate increases sharply with collagen concentration. The gels are easier to destroy by the shear forces at lower concentrations but restore their structure if they are left at rest long enough. This may suggest that intermolecular hydrogen bonds are carried out, as with micromolecular amides, via water molecules.

The main forces that produce the coalescence of the type I fibrillar collagen gel are electrostatic forces, the others contributing in a small extent to its consistency. The collagen fibrils linked by hydrogen bonding and hydrophobic and electrostatic interactions are not stable, being dissociated by variations in temperature, ionic strength, pH, or collagenase [12]. In order to improve mechanical strength, thermal stability, and biodegradation rate, covalent bonds are suggested for collagen gels.

Besides the gels, hydrogels are three-dimensionally hydrophilic polymeric networks obtained by cross-linking of gels. Cross-linking ensures the insolubility of hydrogels in water because of the ionic interaction and hydrogen bonding, providing mechanical strength as well as physical integrity to the polymeric hydrogels [1].

2.1 Methods of Obtaining Collagen Hydrogels

Collagen hydrogels are biomaterials obtained by cross-linking of corresponding gels. Mechanical and biological properties are controllable and usually superior compared to the gels from which they were obtained.

Natural in vivo cross-linking provides mechanical strength and proteolysis resistance to collagen [13]. Used in vivo, collagen biomaterials are subject to enzymatic degradation, which is why they are stabilized by in vitro cross-links, especially with aldehydes [14–16]. Cross-linking methods lead to creation of additional chemical bond between collagen molecules and/or fibrils, increasing mechanical and chemical strength and, consequently, reducing biodegradability.

In vitro collagen cross-linking methods can be classified in two categories: physical and chemical. The main disadvantage of chemical cross-linking is the potentially toxic effect of residual cross-linking agent or of complexes formed in

the process of in vivo degradation. In order to eliminate this disadvantage, physical treatment is applied, including heat-drying and exposure to UV and γ radiation. Both dehydrothermal and UV exposure at 254 nm wave length increase the collagen contraction temperature and also the enzymatic degradation strength. However, these physical treatments cause partial denaturation in collagen [13].

Chemical cross-linking consists of collagen reactions with aldehydes, diisocyanates, acyl azides, polyepoxides, and polyphenolic compounds, which lead to the formation of ionic or covalent bonds between molecules or fibrils. The most used cross-linking agents are aldehydes, especially formic and glutaric. From all cross-linking agents, glutaraldehyde (GA) is the most used due to its high efficiency in stabilization of biomaterials made out of collagen. GA cross-linking involves reactions of the free ε-amine groups of lysine or hydroxylysine from the polypeptidic chains with the GA aldehyde groups [17]. Lysine and hydroxylysine represent 3% from all collagen amino acids and, because of this, approximately 60% of those amino acids residues react with GA under the conditions used to achieve a certain degree of fixation [18].

Although other cross-linking agents are preferred to reduce cytotoxicity, they cannot equal GA in terms of stability [11]. The success of thousands bioprosthesis implanted in last years has shown that GA cross-linking is clinically accepted, despite reported cytotoxicity [16, 19, 20]. Biocompatibility of collagenic materials cross-linked with GA can be increased by lowering its concentration or by combining it with others physical-chemical treatments [21]. As an alternative to aldehyde treatment, resistant collagenic materials can be obtained using hexamethylene diisocyanates (HDC) as cross-linking agents. HDC is solubilized in water with surfactants or dissolved in 2-propanol. It forms bonds with two chemical ε-amine groups passing through urea-like linkages, mainly used to obtain cross-linked gelatin-based plasma substitutes.

Many studies have focused on the use of epoxide compounds (diglycidyl ethylene glycol, polyglycidyl glycol, methylglycidyl ether) [22]. Epoxide compounds react easily with amine groups of lysine, but they also pose the problem of cytotoxicity [23].

Carbodiimide cross-linking, especially with 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC), offers the advantage of forming amide linkages between the carboxyl and amine groups of the collagen molecules without becoming part of the effective linkage. Thus, dysfunctional cross-linking agents are avoided [13].

Collagen gel and collagen gel cross-linked with glutaraldehyde and with carbodiimide obtained in our laboratory are presented in Fig. 1.

Intermediary forming of acyl azide is an alternative method of those with carbodiimide, which has as result amidic bonds introduction [24]. Carboxyl groups are transformed into hydrazide. Then, the reaction with sodium nitrite takes place to form the acyl azide. Otherwise, the diphenylphosphoryl azide modification can be made. Acyl azide treatment increases collagen-glycosaminoglycan matrix resistance for up to 3 months and inhibits calcification in vivo, while collagen treated with glutaraldehyde is completely calcified after 15 days due to calcium fixation at free carboxyl groups [25].

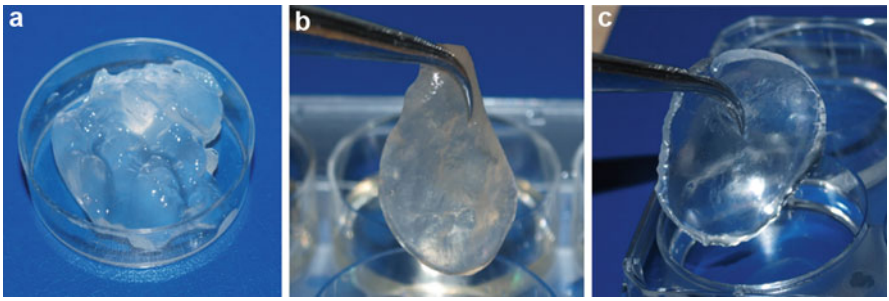

Fig. 1 Collagen gels: (**a**) un-cross-linked and cross-linked with (**b**) glutaraldehyde and (**c**) EDC/NHS

Polyphenols have been used as vegetal tannins for tanning animal skins for a very long time [26]. These are good cross-linking agents due to multiple interactions with proteins, thus increasing the stability of collagen from hydrogels or spongious matrices.

Genipin is a natural cross-linker which demonstrated lower cytotoxicity and better biocompatibility compared with chemically synthetized cross-linking agent [27].

Collagen properties can be controlled by using different type or amount of cross-linkers named before and by varying cross-linking conditions. Cross-linking generally creates a covalently bonded gel that does not deform as a fluid during injection, but it rather fractures and does not recover, leaving a mass of particles.

2.2 Properties of Collagen Hydrogels

Hydrogels are three-dimensional networks made of hydrophilic polymers obtained from gels by covalent bonds cross-linking or by ionic forces, which in aqueous medium swell to an equilibrium value.

Cross-linking degree is one of the most important factors which affects hydrogel swelling. It is defined as a ratio between the number of moles of cross-linker and the number of moles of units that are repeated from the polymer molecule. The higher the degree of cross-linking, the more dense structure and the less intense swelling due to reduction in polymeric chain mobility. The degree of swelling is also affected by the chemical structure of the polymer: hydrogels containing large amount of hydrophilic groups are swelling more intense than those containing hydrophobic groups.

Hydrogel swelling may also be affected by the swelling environment temperature or ionic strength and pH, as well as by other factors [28].

The kinetics of hydrogel swelling can be controlled by diffusion when applying Fick's law or by relaxation when the law is no longer respected. If the diffusion of

water in the hydrogel occurs faster than the relaxation of the polymeric chain, the swelling kinetics is controlled by diffusion.

The mechanical properties of hydrogels are very important for pharmaceutical applications and can be achieved by modifying their cross-linking degree. Increasing cross-linking leads to more consistent but more fragile gels. There is an optimal degree of cross-linking for which the hydrogel is elastic and resistant.

Collagen, alone or in combination with other molecules from the extracellular matrix, plays an important role in the physiology and behavior of cells from connective tissue. Keratinocytes and fibroblasts are important cells involved in healing skin lesions. Therefore, the use of collagen hydrogels as a substrate for the cell culture improves adherence, migration, growth, and cell differentiation under normal and pathological conditions [4].

The interaction between collagen and blood platelets plays an important role in the mechanism of hemostasis induction. Platelets adhere on the collagen surface; their adhesion and aggregation activate clotting and initiate hemostasis. The reaction depends on the cross-linking degree of collagen from hydrogels and on the positive loads localized on the base groups from the side chain. If free collagen carboxylic groups are blocked by chemical processes, more than 98% of hemostatic activity disappears. Hemostasis is dependent also on the conformational structure of collagen. Thus, denatured collagen (gelatin) does not activate platelet aggregation, whereas non-denatured collagen in forms of fibrils can activate platelets, being efficient in hemostasis induction.

Generally, the interactions between collagen and cells are important phenomena in wound healing process and in adult tissue remodeling, collagen inducing differentiation and maintaining cell phenotype [29, 30]. Another important biological property of collagen is biocompatibility, due to its low toxicity and poor immunogenicity. Also, collagen is poorly antigenic. Low antigenicity can be due to the presence of aromatic amino acids, especially tyrosine. In collagen, there is a low quantity of aromatic amino acids, about three residues of tyrosine on a chain. To reduce or eliminate collagen antigenicity, the N-terminal regions of the polypeptide chains are removed during the collagen extraction process.

2.3 Collagen-Natural Polymer for Tissue Engineering

The most recent studies showed a continuing concern about obtaining biomaterials which mimic extracellular matrix for further use in regenerative medicine. The collagen, the main component of skin extracellular matrix, can be used as tissue engineering scaffold in combination with other polymers or cross-linked [27].

Collagen-elastin cross-linked squaric acid created a 3D transparent hydrogel highly resistant to enzymatic degradation to be used in medicine and tissue engineering [31]. Other hydrogels based on collagen, hyaluronic acid (HA), and sericin in different ratios showed that HA played the role of cross-linking agent which were proved to be nontoxic and very consistent against enzymatic treatment [32]. Collagen and chitosan in the presence of α, β-glycerophosphate formed hydrogels which

proved their ability to be biocompatible substrates with L929 cells, being promising scaffolds for tissue engineering [33]. Drug delivery systems and hybrid hydrogels based on collagen such as collagen-hydroxyapatite-alendronate hydrogel for MC3T3-E1 osteoblastic cells [33], collagen-polyvinylpyrrolidone superabsorbent hydrogels cross-linked by γ-irradiation [34], chitosan-collagen coated with poly(L-lactic acid) by electrospinning [35] for tendon regeneration, and collagen-poly(*N*-isopropyl acrylamide) with montmorillonite nanoparticles incorporated hydrogel [36] were also developed.

Our experience in natural collagen hydrogels allowed the development of functional hydrogel scaffolds biocompatible with different types of cells and designed for different tissue engineering applications. These hydrogels are further presented in Sect. 4.

3 Applications of Collagen-Based Substituents in Tissue Engineering and Regenerative Medicine

Collagen is the key component of the extracellular matrix in most tissues and is involved in the maintenance of tissue three-dimensional architecture, as well as in the development of new tissues and organs. Consequently, one of the targets in tissue engineering is to develop substitute biomaterials that can closely resemble the extracellular matrix and, thus, to be integrated both structurally and functionally in the newly formed tissue. Due to the high prevalence of collagen in all tissues and organs, the engineered collagen-based substituents have wide applications, as further described.

3.1 Bone and Cartilage Repair

Collagen is the main structural protein in the extracellular matrix of hard and semihard tissues [37]. Consequently, orientation toward collagen-based biomaterials for cartilage and bone tissue engineering came as a natural choice; however, because collagen alone is not a suitable substituent for bone tissue engineering (BTE) applications in terms of mechanical properties, the usage of a new combination of materials in the pursuit of a more biomimetic scaffold was reported [38]. The team created a nanosized hydroxyapatite (nHA) and collagen-based hydrogel as a support for the proliferation and differentiation of human mesenchymal stem cells (hMSCs) isolated from either adipose tissue (AT-MSCs) or bone marrow (BM-MSCs). Although their hypothesis stated that osteogenic differentiation should be dependent on nHA concentration, the results of the study showed that AT-MSCs display a higher osteogenic potential compared to BM-MSCs, irrespective of nHA amount in the constructs.

Similarly, in 2016, Gurumurthy et al. [39] reported the attempt to find a more suitable scaffold for guided bone regeneration. Since collagen alone is characterized by mechanical weaknesses, composites with elastin-*like* polypeptide (ELP) were

analyzed as a support for human adipose-derived stem cells (hASCs) in osteogenic differentiation processes. After 3 weeks of evolution, the ELP-collagen constructs proved to be superior to pure collagen scaffolds in terms of tensile strength, elastic modulus, osteogenic activity, and mineralization.

A new technique in BTE [40] offers a deeper perspective in long-term repair of bone defects. Using an iterative layering freeze-drying method of assembling gradual amounts of collagen (Col) and hyaluronic acid (HA), the group has created a biomimetic bone substitute which presents a top-bottom gradient of both interconnected porosity and HA content. The similarities with the physiological structure of the bone were easily observed, and the chemical composition resembled the natural model, with $^1/_3$ organic and $^2/_3$ inorganic elements. The biocompatibility of this Col/HA scaffold was assessed via the evolution of a seeded BM-MSCs culture. Compared to a collagen scaffold, the Col/HA composite indicated better rates of success in bone tissue regeneration, and thus, it could be considered an advanced strategy in tissue engineering.

One of the main implementation problems in BTE is to ensure the blood supply to the construct. According to a recent study [41], this issue may have found its solution in cocultivation of cells. As well as bone grafting, bone tissue engineering is a feasible approach toward minimizing extended bone defects in the fields of orthopedics and oncology. In order to regenerate bone fragments, the team studied the advantages of cocultivating endothelial cells together with an osteogenic cell lineage in the context of a mouse calvarial defect model. Using a negative control represented by a pure collagen scaffold, a positive control of a collagen scaffold enhanced with bone morphogenetic protein 7 (BMP-7), and three collagen scaffolds seeded with human osteoblasts (hOBs) only, CD34+ cells only, and a coculture of hOBs and CD34+ cells, respectively, Hertweck et al. concluded through a series of radiographic, histological, immunohistological, and statistical methods that the cocultivation of hOBs and CD34 + cells or even the monoculture of CD34+ cells offers a better perspective in bone regeneration than monocultures of osteoblasts.

More recently, Nguyen et al. [42] reported the analysis of a suitable biomaterial for prevascularized bone fabrication prior to implantation in a patient. The group determined the importance of specific environmental parameters in human umbilical vein endothelial cells (HUVECs) and hMSCs coculture. Different scaffold types, from alginate hydrogels for hMSCs differentiation into osteoblasts to collagen type I hydrogels for HUVECs angiogenesis, were assessed. In addition, shear stress was applied to this coculture system in a tubular perfusion system bioreactor in order to advance the progression toward osteogenesis and prevascularization. Moreover, it was observed that cells attached, proliferated, and differentiated with better rates due to specific peptide sequences as native content of cell-binding sites in collagen fibrils, leading to the conclusion that collagen would be better for future bone tissue engineering applications.

In 2015, Lee et al. [43] studied the fabrication process of biomimetic three-dimensional structures with preosteoblasts and hASCs. Their team engineered a bioink that apart from being nontoxic, biocompatible, and printable, also has cell-activating properties. By pre-cultivating cells in collagen, they enriched the

traditional collagen/alginate composite with extracellular matrix. After being printed, the resulted cell-embedded bioink undergone a cell viability and differentiation study: preosteoblasts successfully started displaying osteogenic activity; whereas hASCs followed a hepatogenic differentiation pathway, expressing liver-specific genes.

Cartilage is an avascular, aneural, and alymphatic tissue, with a very low number of progenitor cells and a very slow turnover of the extracellular matrix. Therefore, this tissue has a very limited auto-regeneration potential and represents one of the most addressed tissues by tissue engineering and reconstruction procedures. In this context, collagen-based biomaterials have been widely used for applications, such as repair of articular cartilage lesions, replacement of intervertebral discs, knee menisci, anatomical disorders of the temporomandibular joint, deformities of the midface and ears, etc.

To address one of the challenges of cartilage engineering, several collagen-mimetic hydrogels with chondrogenesis-inducing properties have been proposed. For example, Parmar et al. suggested a novel biodegradable collagen hydrogel with incorporated heparin-binding, integrin-binding, and hyaluronic acid-binding sequences at the backbone of a streptococcal collagen-*like* 2 protein. Metalloproteinase 7 (MMP7) and aggrecanase (ADAMTS4)- cleavable peptides were later used in the process as cross-linkers. Their conclusion was that this new collagen-based hydrogel can be used for cartilage regeneration therapies, since it promoted cell viability, cell adhesion, and chondrogenesis [44].

One of the treatment courses adopted for focal cartilage lesions involves matrix-induced chondrocytes implantation (MACI). As this method requires autologous chondrocytes prone to dedifferentiation during in vitro expansion, Fensky et al. proposed the implantation of predifferentiated MSCs seeded in a type I collagen hydrogel. The MSCs were cultured in collagen hydrogels, and predifferentiation was initiated by adding TGF-β1 in the culture media. After 10 days, the hydrogels were switched to a TGF-β1-free media for another 11 days. In both histochemical assay and chondrogenic markers, gene expression confirmed the evolution of chondrogenesis. Therefore, the collagen hydrogel could represent a reliable method in delivering predifferentiated cells to the needed implantation site [45]. Additionally, Chen et al. [46] concluded that a type I collagen hydrogel seeded with mesenchymal stem cells isolated from the Wharton's jelly of human umbilical cord (UC-MSC) could be a suitable 3D model for cartilage healing.

The suitability of collagen hydrogels in CTE was also confirmed in a study focused on material's immunomodulatory properties [47]. The group investigated the immunogenicity of neonatal rabbit chondrocytes seeded in a collagen type I hydrogel. Even though the immunogenicity markers showed a tendency to increase over the first 14 days of in vitro culture, after 28 days, the immunogenic effects were lower. The collagen hydrogel promoted the synthesis of extracellular matrix over the 28 days in culture. This led to the accumulation of extracellular matrix, and it was suggested that it isolated the seeded cells from the host immune cells and from the hydrogel itself, providing some immunogenicity-reducing effects. In addition, in 2016 Yang et al. [48] published a study that compared the evolution of

chondrogenesis and the secretion of immunoregulatory factors of MSCs in 2D and 3D culture. The cells expanded in the collagen hydrogels (3D) showed higher chondrogenic markers at gene and protein levels of expression than the ones on plastic (2D), simultaneously with an enhanced secretion of immunoregulatory factors. This could suggest that the collagen hydrogel promoted the chondrogenic differentiation of MSCs.

3.2 Muscle Tissue Repair

Collagen constitutes 1–2% of the muscular tissue, where it serves as a major component of the endomysium. Several studies have been performed in order to reconstruct muscle tissue assisted by collagen substituents, as further described. Recently a study was conducted regarding the usage of vascularized tissue scaffolds in large volumetric muscle defects [49]. Working on a rat biceps femoral model, the team developed a series of vascularized collagen hydrogels with adipose-derived microvessels. After seeding these scaffolds with myoblasts and implanting them in the existent limb injury, Li et al. observed the revascularization and muscle regeneration processes, as well as the differentiation of myoblasts in myotubes. However, as compared to a vascularized scaffold only, which showed a similar regeneration rate after a 2-week evolution, the team concluded that while the vascular network of the construct may support the regeneration of volumetric muscle defects, other factors have an important role as well.

With respect to the cardiac muscle, studies have been developed to test the efficiency of hybrid hydrogels based on collagen in myocardial regeneration. Injectable bioactive hydrogels were developed from thiolated collagen (Col-SH) by adding multiple acrylate containing oligo(acryloyl carbonate)-b-poly(ethylene glycol)-b-oligo(acryloyl carbonate) (OAC-PEG-OAC) copolymers for improving the material's mechanical properties [50]. The cellular lineage selected for this study consisted of BM-MSCs, due to their rapid spreading rate and extensive network-forming capacity. After the implantation of BM-MSC-encapsulating hybrid hydrogel in a rat infarction model, Xu et al. observed a significant improvement in cardiac function in the case of the hydrogels as compared to the PBS control. Moreover, the echocardiography analysis showed an increase in the ejection fraction at 28 days, while the histological assessments demonstrated a decrease in the infarct size and an increase in ventricular wall thickness.

More recently, von Marion et al. [51] published a study regarding a different method of addressing cardiac stem cell therapy by culturing cells directly in the biomaterial for better survival, proliferation, and differentiation rates. Cardiomyocyte progenitor cells (CMPCs) were seeded in a unidirectional constrained and a stress-free collagen hydrogel. The three-dimensional environment highly supported cellular growth and maturation, and an enhancement was observed in specific markers (Nkx2.5, myocardin). The proof that the CMPCs were actively involved in the matrix secretion and remodeling processes was given by levels of collagen type I, collagen type III, elastin, fibronectin, and matrix remodeling enzymes. Furthermore, when

constrained, CMPCs became mechanosensitive, adopted a rod-shaped morphology and responded to mechanical stimuli in addition to developing sarcomeres and contractility.

In 2017, Ketabat et al. [52] identified collagen and alginate injectable conductive hydrogel systems as promising candidates for cardiac muscle regeneration in terms of cardiomyocyte viability and syringeability. Other tissue engineering applications of such hydrogels rely on their specific property that allow delivery to the requested site through a catheter. Collagen is therefore used for its self-assembly characteristic, resulting fibrous forms upon warming up to 37 °C, while alginate is recommended for its non-thrombogenic nature.

3.3 Nerve Tissue Regeneration

Currently, nerve injuries or diseases that affect the nervous system are found more and more often and seriously affect patients' lives. These nerve injuries could be efficiently addressed by modern strategies in tissue engineering, namely, by designed scaffolds that would represent the necessary support for nerves to regenerate. A few of these strategies are further discussed.

In 2015, a study regarding a novel combination of PuraMatrix 3D nanofibrous hydrogel and a honeycomb collagen sponge in creating a scaffold suitable for neuronal regeneration after complete transection of the spinal cord in adult rats was published. After the implantation of the construct in the 5 mm spinal gap, its evolution was recorded during 24 days to 4 months, as compared to the PBS-injected control group. The histological and western blot analyses have indicated the migration of both neurons and astrocytes toward the implant site, as well as their differentiation and maturation stages, therefore suggesting functional recovery, spinal repair, and neuronal regeneration [53].

Using carbon nanotubes and collagen in generating three-dimensional microenvironmental conditions for MSCs in neural tissue regeneration, Lee et al. [54] highlighted once again the impact of collagen scaffolds on bioengineering. Studying the differentiation process of MSCs in neural lineages, the team has selected collagen as the ideal support for MSCs growth and expression of neural phenotypes, while the addition of small amounts of carbon nanotubes (0.1–1 wt%) has improved cellular proliferation rate. Moreover, CNTs were associated with improvements in both expression of neuronal markers and secretion of neurotrophic factors, especially nerve growth factor and brain-derived neurotrophic factor.

Similarly, Park et al. [55] introduced the concept of 3D collagen scaffolds for human umbilical cord blood (UCB) cells in order to promote the secretion of therapeutic factors, such as neurotrophic factors. Collagen proved to be an advantageous biomaterial, not only being a suitable 3D microenvironment but also stimulating the secretion of neurotrophins, nerve growth factor, brain-derived neurotrophic factor, and ciliary neurotrophic factor. Moreover, the 3D scaffold has also been described as an efficient reservoir of neurotrophic factors by storing and slowly delivering them toward the target cells. To confirm their hypothesis, Park

et al. have facilitated indirect interaction of UCB environment with human neural precursor cells, observing afterward neurite outgrowth. Future implications of such scaffolds include therefore neural repair and regeneration processes.

3.4 Vascular Grafts

Aiming to study vascular biology in health and disease, Roberts et al. published in 2016 a study concerning the process of generating microvessels by seeding endothelial cells in a microfluidic channel embedded with a native type I collagen hydrogel. Their three-dimensional model serves as a solution for the inadequate planar cell culture and uses injection molding methods to generate engineered blood vessels. The study of seeded HUVECs has already offered an insight in pericyte migration, platelets adhesion to activated endothelium, fluid shear stress modulation of endothelial activity, and von Willebrand factor (VWF) secretion and assembly. Moreover, by adding parenchymal cells in the collagen matrix, the researchers have created a tissue microenvironment which allows them to further study processes related to the intestinal lining, lung alveoli, kidney tubule, and many others [56].

The developing process of an injectable allogenic collagen-phenolic hydroxyl (collagen-Ph) hydrogels in mice that supports de novo generation of a three-dimensional vascular network was recently documented [57]. Specifically, they injected in subcutaneous murine models a prepolymer solution of collagen-Ph, human blood-derived endothelial colony-forming cells (ECFCs), bone marrow-derived mesenchymal stem cells (MSCs), horseradish peroxidase, and hydrogen peroxide and analyzed the course of tissue forming. After 7 days, the ECFCs have generated extensive vascular networks and functional anastomoses with the existing vasculature of the host tissue; the collagen has improved MSCs differentiation, while phenolic hydroxyl has favored an increase in the number of adipocytes present in the targeted tissue [57].

3.5 Corneal Reconstruction

The cornea may suffer from diseases, injury, infections, or inflammation, and these can lead to the need of a corneal replacement. To avoid total replacement by surgery, modern approaches in tissue engineering identified the opportunity to use adapted hydrogels to assist corneal regeneration. Latest research in this field is further presented.

In 2016, Rafat et al. [58] assessed the suitability of collagen-based hydrogels as biomaterials in corneal regeneration. Their team engineered a construct with a transparent core and an adjustable periphery characterized by faster degradability rates. The material was used in in vitro cultivation of human epithelial cell populations and transplanted in an in vivo mice model. After a 3 months' time evolution, the collagen construct was declared suitable for corneal transparency restauration, maintaining the overall corneal shape and integrity.

Previously, other studies [59] presented an alternative to the cross-linkage method of generating transparent collagen hydrogels. By substituting the usage of *N*-(3-dimethylaminopropil)-*N*′-ethylcarbodiimide (EDC) with a sterically bulky carbodiimide, *N*-cyclohexyl-*N*′-(2-morpholinethyl)carbodiimide metho-p-toluensulfonate (CMC), the group obtained corneal replacements with longer, easier to control gelation time, as well as superior resistance to collagenase. Liu et al. [60] started using collagen in developing corneal substitutes since 2008. Their hydrogels were synthesized as interpenetrating polymeric networks (IPNs) and were constituted of 1-ethyl-3-(3-dimethyl aminopropyl) carbodiimide, *N*-hydroxysuccinimide cross-linked porcine atelocollagen, and poly(ethylene glycol) diacrylate cross-linked 2-methacryloyloxyethyl phosphorylcholine. Compared to each individual compound, the hydrogel presented greater mechanical strength, as well as enzymatic stability and low UV degradation rates. Due to collagen, the corneal substitute appeared to be cell-friendly, promoting nerve ingrowth and regeneration. Moreover, its optical properties resemble the human model. When implanted in pigs, the allografts indicated in vivo compatibility, the experiment being declared a success.

After previously postulating porcine collagen hydrogels as corneal substitutes, another study [61] assessed the potential use of recombinant human type I and type III collagen in such applications in order to minimize the possible immune reactions toward animal origin implants. By cross-linking the collagen fibrils with 1-ethyl-3-(3-dimethyl aminopropyl) carbodiimide (EDC) and *N*-hydroxysuccinimide (NHS), the team created a corneal substitute with light transmission properties comparable to superior to that of a human model. Not only that these substitutes had adequate tensile strength and elasticity for surgical procedures, but type III collagen proved to be superior in terms of mechanical characteristics. During a 12-month post-implantation assessment in pigs, the hydrogels maintained their optical clarity, promoted regeneration of corneal cells, nerves, and tear film and proved to be eligible for further clinical applications.

McLaughlin et al. [62] addressed the problem of tissue regeneration by extracellular mimics in the context of cornea, a three cellular layered structure in a hydrated extracellular matrix, delimited by a nonkeratinizing epithelium and an inner endothelium. Proposing a corneal substitute made out of carbodiimide cross-linked porcine type I collagen, they have demonstrated that simplicity in fabrication might be the key to future biomaterial applications. During a 12-month integration and development of the collagen implant in the host tissue, it was observed that the substitute supported the regeneration of corneal cells, nerves, and the tear film. Moreover, it had been described as maintaining its optical clarity.

3.6 Other Biomedical Applications

Collagen scaffolds can also be used as apoptotic sites when conjugated with cyclopamine, according to a study of Jain et al. published in 2014. The team analyzed the migration of the cells constituting a glioblastoma, an aggressive brain tumor which invades adjacent cerebral regions along white matter tracts and blood

vessels. After engineering aligned polycaprolactone-based nanofibers as an invasion site, they mediated the transfer of the tumor toward the extracortical cyclopamine drug-conjugated, collagen-based hydrogel. Cyclopamine was preferred because it only affects cells which are dependent on the sonic hedgehog pathway of survival, i.e., cancer stem cells. Tumor loads were significantly higher in the case of nanofiber implants compared to smooth film or empty conduit implants. Moreover, tumor loads outside of the collagen-based hydrogel were significantly lower in the case of nanofiber implants [63].

In 2013, Rao et al. developed an unprecedented study of a series of three-dimensional collagen – hyaluronan composite hydrogel in order to achieve an accurate model of glioblastoma tumor cell migration. Their work focused on using biomaterials to understand tumor cell biology rather than promote tissue engineering. Collagen scaffolds were selected due to the material's association with cell migration, collagen types I, III, and IV being found in glial lamina externa and vascular basement membranes, while collagen types I and III as well as hyaluronan are the main constituents of the native brain extracellular matrix. The team observed that glioblastoma migration occurs in inverse function of hyaluronan concentration; therefore hyaluronan has a delaying effect on cell movement [64].

4 Original Collagen Hydrogels Designed and Tested for Adipose and Cartilage Tissue Engineering

Based on the positive results reported by other groups and on the versatility of collagen-based hydrogels for different tissue engineering applications, our group has studied two different composites designed for cartilage and soft tissue reconstruction.

4.1 Collagen-Sericin Hydrogels

Hydrogels based on type I fibrillar collagen (Coll) with different ratio of silk sericin (SS) presented a superporous and absorbent structure (Fig. 2). The pore size varied between 2 and 90 μm, the structure being denser with increasing amount of sericin. The absorbent capacity showed values between 3000% and over 4000% at acidic, alkaline, and neutral pH and classified hydrogel as being very absorbent. Even the high amount of sericin showed more compact structures. The mechanical properties and biodegradation rates demonstrated that the best scaffold was Coll:SS = 5:2 ratios [65]. The physicochemical results were confirmed by biological ones which showed that preadipocytes colonizing the scaffold containing 40% sericin, being a good candidate for future applications in soft tissue engineering [66].

This validated composition of CollSS hydrogel was developed for adipose tissue engineering (ATE) and revealed good biocompatibility and supported differentiation of human adipose-derived stem cells (hASCs) [67]. Silk sericin (SS) is a natural sticky protein isolated from *B. mori* silk fibers, which proved to be responsible for

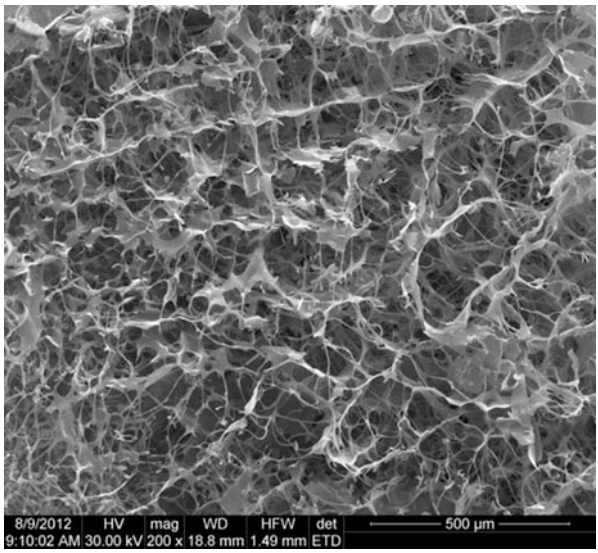

Fig. 2 SEM image of collagen: sericin (5:2) hydrogel, x 200

proliferation and attachment of several mammalian cell lines [68] as well as for the activation of collagen production, both in vitro and in vivo [69].

4.2 Collagen-Polysaccharides Hydrogels

Furthermore, in order to direct this biocompatible composite (CollSS) toward cartilage tissue engineering (CTE), two pro-chondrogenic molecules, components of cartilage extracellular matrix – hyaluronic acid (HA) and chondroitin sulfate (CS) – were added in the composition, resulting in a pro-chondrogenic collagen hydrogel (CollSSHACS). Several ratios between HA and CS were tested to identify the most efficient one for CTE: CollSS-10%HA, CollSS-5%HA, CollSS-10%CS, and CollSS-5%CS. HA increased the thermal stability of scaffolds; the absorbent properties showed a higher capacity to uptake water (4200–4300%) than the control samples (CollSS) and the pore size between 20 and 150 µm, being larger for CollSS samples which contain HA and smaller for samples which contain CS [70].

Cytocompatibility studies with hASCs and their differentiation toward the cartilage lineage revealed the collagen hydrogel improved with 10% HA and 5% CS to be the most equilibrated formula to support cell proliferation [70] and hASCs chondrogenesis during in vitro studies. Briefly, 3D cell-scaffold culture was achieved by seeding hASCs in CollSSHACS and then exposed to chondrogenic induction cocktail for 28 days. The in vitro differentiation process was monitored at 7, 14, and 28 days post-induction. Scanning electron microscopy (SEM) revealed that cells distributed in the volume of the hydrogel through the network of pores and adhered to the CollSSHACS better than to control Coll, probably due to the sticky

properties of sericin. Gene expression studies revealed upregulated chondrogenic markers such as SRY (sex determining region Y)-box 9 (Sox9) and cartilage oligomeric matrix protein (COMP). These results were also confirmed at protein level by confocal microscopy.

To conclude our experience with collagen hydrogels, we have evaluated hASCs/CollSS bioconstruct for ATE [67] and hASCs/CollSSHACS for CTE. Results indicated in both cases the positive influence of sericin on the interaction between hASCs and the surface of the hydrogels and on the differentiation processes. Evaluation by immunohistochemistry and microscopy showed the formation of cellular aggregates in CollSSHACS, which is specific for the first steps of chondrogenesis. Nevertheless, in the absence of HA and CS specific chondrogenic inducers, the conditions offered by CollSS hydrogel favor hASCs differentiation toward the adipogenic lineage, thus confirming CollSS to be appropriate for soft tissue engineering applications.

5 Conclusions

Collagen-based hydrogels incorporating other natural polymers (derived from extracellular matrix tissue) showed very good biocompatibility with different types of cells, but request controllable biodegradability and improved mechanical properties using suitable cross-linker agents (preferably natural). The hydrogels consisting in collagen and synthetic polymer have controllable physical-chemical properties but poor biocompatibility and request surface functionalization with natural polymers in order to improve their biocompatibility. Biopolymers such as hyaluronic acid, chondroitin sulfate, and sericin in combination with collagen formed 3D hydrogels with high biocompatibility and potential to support cells differentiation. Furthermore,

CollSS could prove useful for soft tissue engineering, while CollSSHACS could be a good candidate for cartilage reconstruction.

6 Future Scope

For future studies, more attention should be focused on smart biomaterials such as drug delivery systems with antimicrobial properties based on collagen hydrogels. The drug delivery systems request complex structure so that the drug can be released from hydrogels in a controlled way to avoid the risk of not being effective from the pharmaceutical point of view. A high amount of drug could be toxic for cells – the hydrogel will not be biocompatible, while a small amount of drug would not influence the biocompatibility nor be effective for the proposed aim.

Other challenge in tissue engineering is the risk of infection at the tissular level. For this reason, we focused to establish a balance between antimicrobial and biocompatibility properties, using natural ingredients such as essential oils and

zeolite [71]. Previous results showed that it is possible to open such a "barrier" but extensive research needs to be performed in the future.

Another opportunity to further improve the collagen hydrogel would be to bring together the benefits of collagen with the benefits of autologous platelet-rich plasma (PRP). Rich in growth factors that positively influence cell growth, proliferation, adhesion, and other cellular processes, PRP would ensure better biocompatibility, lower inflammatory potential, and better acceptance rate at the implant site of collagen. One recent study [72] approached this idea and used it to create a collagen-based construct dedicated for skin regeneration. Researchers developed a type I collagen, fractionated platelet-rich plasma (PRP)-supplemented scaffold, able to recruit dermal stem cells from adjacent tissue, fully disclaiming the need of cell seeding. As compared to a collagen – fetal bovine serum control, the new biomaterial proved to be better when implanted into rat wound models in terms of epithelialization and neovascularization. Not only the number of recruited stem cells was higher when PRP was used, but also the dermis-*like* tissue formation proceeded at a faster rate, leading to hair growth and sweat gland production [72].

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Chitosan-Based Hydrogels: Preparation, Properties, and Applications

56

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Contents

Abstract

Chitosan is a hydrophilic polysaccharide obtained by partial deacetylation of chitin, which is one of the most popular biopolymers. Chitosan is well known for its favorable properties including biocompatibility, biodegradability,

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antibacterial, and biological activity, as well as its renewable character. Thanks to those features chitosan's popularity in various applications ranging from food industry to tissue engineering is constantly growing. The following chapter will more closely consider fabrication, properties, and specific applications of chitosan-based hydrogel networks. Methods for chitosan preparation will be summarized, followed by detailed characterization of chitosan properties. Strategies for their improvement and fabrication of chitosan derivatives will be discussed as well. Next, attention will be drawn to preparation of chitosan-based hydrogels via chitosan crosslinking. Both chemical and physical crosslinking methods will be considered with special emphasis on comparison between the two crosslinking methods and recent advancements in application of novel biocompatible crosslinkers. This chapter will also take a closer look at formation of stimuli-responsive (especially pH- and temperature-sensitive systems) and injectable hydrogels. Utilization of chitosan hydrogels in tissue engineering will be highlighted together with different techniques for fabrication and construction of three-dimensional scaffolds. Finally, other applications of chitosan-based hydrogels and their composites will be summarized.

Keywords
Chitosan · Hydrogels · Polysaccharides · Biomaterials · Tissue engineering

1 Introduction

Synthetic products, including synthetic polymers, are widely used in many applications due to their favorable and – most importantly – consistent/reproducible properties. However, being mostly derived from fossil fuels, their high overall usage worldwide adversely affects the environment. Given the environmental concerns raised in past years, turning into more eco-friendly polymers is becoming crucial.

Nature gives us many interesting options within polymer family [1, 2], such as collagen, gelatin, alginate, chitin, to name a few most popular, that could reduce negative environmental impact. Unfortunately, the transition from synthetic to bio-based polymers is not easy due to the obvious differences in structure and resulting properties between these two groups. Obtaining bio-based materials with functionality comparable to that of the synthetic ones is currently one of the pressing matters in materials science.

Generally, chitosan possesses structure and properties that are similar to those of glycosaminoglycan (GAG) – natural polysaccharide and a major component of extracellular matrix (ECM). Being nontoxic, antibacterial, biodegradable, and biocompatible, chitosan can be used in many applications ranging from the food industry to tissue engineering. PubMed search of the term "chitosan hydrogel" gives 1382 results, and the term "chitosan" alone appears in the PubMed database 20,041 times (as of mid-2017). That shows how much attention this versatile polymer has attracted recently.

This chapter gives insight into fabrication, properties, and specific applications of chitosan-based hydrogels. Chitosan preparation methods, properties, and example derivatives are presented in more details. Formation of hydrogel networks based on chitosan and features of stimuli-responsive systems is also discussed, followed by examples of recent research on novel chitosan solutions for tissue engineering, drug delivery, wound management, and water purification.

2 Chitosan

Chitosan is a derivative of chitin – the second, after cellulose, most widespread natural polymer. The term "chitosan" refers to the whole family of chitin-derived polymers with different deacetylation degree, starting from 50% [1, 3]. Going into details, it is a linear, semicrystalline polyaminosaccharide typically composed of two repeating units: (1 → 4)-2-acetamido-2-deoxy-β-$_D$-glucan (*N*-acetyl $_D$-glucosamine) and (1 → 4)-2-amino-2-deoxy-β-$_D$-glucan (*N*-acetyl $_D$-glucosamine). Chemical structures of chitin and chitosan are shown in Scheme 1. The ratio of the two main units, D-glucosamine and N-acetyl-D-glucosamine, determines the degree of deacetylation – one of the most important parameters affecting final properties of the chitosan material [4–6].

2.1 Preparation Methods

Chitin, poly(β-(1→4)-*N*-acetyl-$_D$-glucosamine), is a polysaccharide available in large amounts in nature, mainly as a component of exoskeletons of crustaceans, fungi, and insects – Table 1.

The most popular sources of chitin raw material are crab and shrimp shells – their rigid shells are composed of complex chitin network with proteins and calcium salts deposits [8]. Therefore, in order to isolate chitin from the shells, those components have to be removed by deproteinization and demineralization steps, respectively. Both can be realized using different methods, namely, chemical and biological extraction, with the latter favored in eco-friendly approach [9, 10]. Their detailed review has been recently given by Younes and Rinaudo [11].

Demineralization is achieved by the acidic treatment that leads to the transformation of mineral constituents (mainly calcium carbonate) into salts that are soluble

Scheme 1 Chemical structure of chitin and chitosan

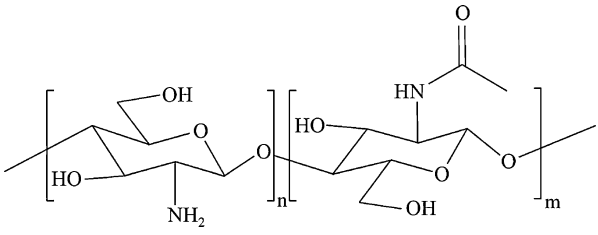

Table 1 Sources of chitin and chitosan. (Reprinted with permission from [7]. Copyright © 1990, American Chemical Society)

Sea animals	Insects	Microorganisms
Annelida	Scorpions	Green algae
Mollusca	Spiders	Yeast (β-type)
Coelenterata	Brachiopods	Fungi (cell walls)
Crustaceans:	Ants	Mycelia Penicillium
Lobster	Cockroaches	Brown algae
Crab	Beetles	Spores
Shrimp		Chytridiaceae
Prawn		Ascomydes
Krill		Blastocladiaceae

in water and thus can be easily removed by filtration and subsequent washing. The reagent is usually diluted hydrochloric acid; however, other options are possible. Next step – deproteinization, i.e., removal of proteins, performed in alkaline conditions, is especially important for the further use of chitin derivatives in biomedical applications, as shellfish are known allergen. Proteins removal is performed in various base solutions, e.g., with sodium hydroxide being the most popular, at different reagent concentration, treatment temperature, and time duration. Reaction conditions need to be adjusted to assure the successful destruction of strong, chemical bonds between chitin and proteins [11, 12].

A biological approach to chitin extraction involves the use of specific enzymes or microorganisms and is considered to be faster, safer, and less destructive in terms of the physicochemical properties of native chitin. During deproteinization and demineralization also some lipids and pigments are eliminated, and if necessary, further decolorization and purification are performed to obtain high-quality, colorless product [11].

The neat chitin is a rigid, highly crystalline polymer with high molar mass from around 200 Da to over 1000 kDa, insoluble in most of the solvents and difficult to process. However, it can be partially deacetylated and thus converted to chitosan – derivative with a larger amount of amino groups and increased solubility. This process can be realized via chemical or enzymatic routes [4].

Chemical deacetylation of chitin is usually performed using alkaline solution, either hetero- or homogeneously. The former is based on the few-hour treatment with concentrated hot NaOH solution. The latter also involves treatment with concentrated NaOH solution but at room temperature and with subsequent dissolution in ice at 0 °C. The products of heterogeneous and homogeneous *N*-deacetylation have different solubility and deacetylation degrees (DD): insoluble with DD as high as 85–100% or soluble with DD around 50%, respectively [11]. Chitosan obtained by hydrolysis via chemical processing of chitin in concentrated NaOH has lower, largely distributed average molar mass.

Chemical deacetylation, however inexpensive and suitable to mass production, has also some drawbacks including possible damages to the polymer backbone and negative environmental impact due to the high energy consumption, use of large

amounts of concentrated alkalis, and a wide spectrum of soluble and insoluble reaction by-products.

Alternatively, enzymatic-mediated deacetylation can be used [13–15]. This method is based on hydrolysis of *N*-acetamido bonds of chitin substrate, catalyzed by chitin deacetylase, the enzyme found in fungi and insects. The biggest advantage of biotransformation of chitin to chitosan, when compared to conventional chemical process, is the higher molar mass and better molecular structure of the final product. Enzymatic treatment is much less aggressive – it allows to preserve original polymer structure, but at the same time, it is difficult to achieve a high degree of deacetylation, especially considering crystalline nature of chitin chains configuration and limited accessibility of the *N*-acetyl $_{D}$-glucosamine units. Therefore, some modifications of chitin such as aiming at reducing its crystallinity and opening up the structure are necessary [15, 16].

2.2 Chitosan Properties

One of the key parameters characterizing chitosan and distinguishing it from chitin is the degree of deacetylation (DD) [17]. The DD value shows the ratio of $_{D}$-glucosamine to the sum of $_{D}$-glucosamine and *N*-acetyl $_{D}$-glucosamine, i.e., how many (in molar percentage) of monomeric units have amino groups. The DD of chitosan is in the range of 50–100%, with the latter being for fully deacetylated chitin [17, 18]. The average molar mass of chitosan is usually in the range of 50–2000 kDa.

The degree of deacetylation, together with molar mass, directly affects physicochemical (e.g., solubility and chain conformation) and biological properties of chitosan [18]. The degree of deacetylation is directly proportional to the solubility, viscosity, biocompatibility, and other biological properties, such as mucoadhesive, analgesic, antibacterial, and hemostatic activity. At the same time, a decrease of DD leads to decrease of chitosan crystallinity and biodegradability. In the case of molar mass, inverse proportionality is observed for biodegradability and antioxidant activity [19].

Unique properties of chitosan emerge mostly from the presence of amino groups in its structure. Chitosan cannot be dissolved in water, aqueous bases, or organic solvents but dilute acidic solutions (pH < 6) protonate its amino groups, making it a cationic polyelectrolyte. The transition between soluble and insoluble (positively charged and not-charged) chitosan state occurs in the pH range of 6–6.5 at the specific pKa value. The protonation degree depends also on the pK_a of the acid used as a solvent and affects the biomaterial properties [20, 21]. Hence, it is the presence of the amino groups that allows controlling "charged state" and the properties of chitosan [19].

Another advantage arising from the presence of the amino groups is the chitosan's ability to form complexes with, for example, metal ions [4, 22]. Moreover, once the polycation is formed, it can further form ionic complexes with negatively charged synthetic polymers, like poly(acrylic acid) or anionic molecules, such as lipids, proteins, and DNA [22].

Beside amino groups, chitosan chains have also hydroxyl groups. Both of them enable covalent bonding and therefore, by introducing various species along the polysaccharide backbone, widen the possible applications spectrum. The alcohol groups allow nonspecific reactions, such as etherification and esterification, while the amino groups can undergo reductive amination to have aldehyde functions [4, 22].

From the biomaterial perspective, chitosan is an extremely interesting natural polymer exhibiting variety of useful properties. Its remarkable biological features include antibacterial [23], antifungal [24], mucoadhesive [25], analgesic [26, 27], and hemostatic [28, 29] properties, as well as biodegradability [30] and biocompatibility [31].

The biodegradability of chitosan depends mostly on its degree of deacetylation. However, it is also affected by the chitosan molar mass, dispersity, and the distribution of *N*-acetyl $_{D}$-glucosamine residues. In the human body, chitosan can undergo enzymatic degradation by lysozyme, acid, gastrointestinal enzymes, or colon bacteria [30]. Breakage of glycosidic bonds results in the formation of different-length oligosaccharides that, being nontoxic, can be either incorporated in the metabolic pathways or excreted by renal filtration. Interestingly, the amino groups protonation may also occur due to absorption of proton ions released in the inflamed area, what results in chitosan analgesic and anti-inflammatory effects [26, 27].

2.3 Chitosan Derivatives

Chitosan is a remarkable polysaccharide with many interesting properties; however, there is still room for improvement. Researchers are especially interested in increasing its water solubility and finding new applications by altering already favorable properties of the polymer. Chitosan derivatives can be obtained by graft copolymerization, carboxymethylation, thiolation, O-hydroxyalkylation, and quaternarization [32, 33].

Covalent linkage of molecules onto chitosan backbone is possible due to the presence of two types of reactive functional groups, amino and hydroxyl, within its structure. Polymers grafted onto chitosan can form cationic or polyampholyte polymers. Grafting can be realized using redox or photoinitiation. Among grafting initiators, the most common ones are cerium (IV) ammonium nitrate, potassium persulfate, and ammonium persulfate. Grafting usually proceeds via direct oxidation or complex formation [34].

The grafting yield, the chemical structure, and the physical form affect solubility and swelling behavior of the final product. Graft copolymerization of (2-diethylamino ethyl methacrylate) (DEAEM) onto chitosan using redox initiation with potassium persulfate was studied under homogenous and heterogeneous conditions, in three different physical forms [34]. Achieved grafting yield ranged between 31% and 54% and appeared to control the solubility of the final product in acidic solutions.

Carboxymethylation can be realized by different chemical routes resulting in carboxymethyl chitosans (CMCS) with varying properties. The reaction of CS with glyoxylic acid in slightly acidic medium formulates N-CMCS. Strongly alkaline medium is used to prepare O-CMCS – an amphiprotic ether derivative. N,N-di-CMCS is prepared in acidic medium, has the ability to chelate metal ions, and possesses a good film-forming ability and osteoinductive properties. The most desirable for biomedical applications is N,O-CMCS – hydrophilic and amphoteric polyelectrolyte derivative, that is biocompatible, has enhanced antibacterial activity and gel-forming ability [35, 36]. Carboxymethyl chitosan is often used as nanoparticles for applications concerning the controlled delivery of active molecules [37, 38]. For example, Teng et al. [39] developed CMCS-soy protein complex particles that were able to encapsulate vitamin D_3 and release it in a controlled manner. The usability of CMCS nanoparticles crosslinked with calcium ions also for oil-spill treatment was demonstrated by Kalliola et al. [40] in their pH sensitive system.

Thiolation, by introducing –SH groups to the polymer backbone, enhances solubility, mucoadhesive, and cellular permeation properties of chitosan. The covalent attachment between the amine group and the mercaptocarboxylic acid realized using carbodiimide (EDAC) and N-hydroxysuccinimide (NHS) allows chitosan modification with thiol groups. Using coupling reaction of a 3-mercaptopropionic acid and CS/EDAC complex, Ko et al. [41] synthesized thiolated chitosan monolayer for cell-based chips in vitro analysis tool. Later, Esquivel et al. [42] adopted the synthesis method to fabricate thiolated chitosan nanoparticles crosslinked by ionic gelation with tripolyphosphate (TPP).

Quaternized chitosan derivative, *N*-(2-hydroxypropyl)-3-trimethylammonium chitosan chloride (HTCC), was shown to be antibacterial and antifungal. It was also proven [43] that HTCC possesses the ability to bind high and low molar mass heparin, what may be exploited in controlled inhibition of the anticoagulative activity of heparin. HTCC-heparin complexes were relatively small, with low polydispersity when compared to heparin aggregates formed when protamine sulfate was used. Li et al. [44] synthesized *O*-quaternary ammonium *N*-acetyl thiourea chitosan bearing double functional groups, that has improved water solubility over a wide pH range. Moreover, grafting of double functional groups, i.e., quaternary ammonium and acyl thiourea, enhanced its antibacterial activity.

3 Hydrogel Formation via Crosslinking of Chitosan

Hydrogels are three-dimensional (3D) polymer networks characterized by high water content and the resulting high flexibility. Hence, being soft and pliable, they naturally mimic many tissues of the human body. In terms of mechanical properties, hydrogels are especially similar to soft tissues. Their viscoelastic nature prevents adverse effect on the surrounding host tissue after implantation, and together with other desirable properties like biocompatibility, functionality, and reversibility, makes them important and extremely interesting part of biomaterial group [19, 45].

Hydrophilic groups within hydrogel polymer network enable high absorption of water-based liquids. Increased water content results in swelling and expansion of the hydrogel volume. Water molecules in hydrogel structure exist in three different states: as free, intermediate, and bound molecules [46]. The amount of free water molecules is dictated by the hydrogel structure – the more compact structure, the less amount of free water it contains. Weak interactions between functional groups of polymer chains and water molecules form intermediate water, while bound water is a result of strong hydrogen bonding between the polymer and water molecules.

In general, crosslinking improves mechanical properties and increases hydrogel stability by interconnecting molecules. At the same time, it reduces the number of available functional groups, thus limiting modification possibilities, decreases polymer degradability, and changes rheology properties that can cause processing difficulties [47]. There are many different methods to prepare chitosan-based hydrogels, but each one requires some steps to ensure hydrogel network stability, i.e., chitosan hydrogels have to be physically or chemically crosslinked. The stability and reversibility of hydrogel system are determined by the crosslinking method.

3.1 Physical Crosslinking

Formation of stable, however nonpermanent, hydrogel networks exploits physical interactions, resulting from physical domain junctions, hydrogen bonding, hydrophobic association, chain aggregation, crystallization or ionic complexation [45, 46]. Physical crosslinking of chitosan hydrogels usually occurs in response to specific conditions, e.g., temperature or pH and might be affected by the polymer concentration and the number of other components. Gelation is a complex problem; due to specific nature of the chitosan molecule, many interactions are involved at the same time, affecting sol-gel transition.

In the case of thermogels, the temperature change is the stimulus triggering gel formation. It was reported [48] that by adjusting the degree of deacetylation, pH of the hydrogel solution, the glycerophosphate concentration, and the chitosan's molar mass, it is possible to modulate gelation temperature. Depending on the temperature, the polarity of the chitosan chains and other possible moieties introduced into the hydrogel system changes. Therefore, also possible hydrophobic and hydrogen bonding interactions are affected, and the gel is formed by heating of the solution. Chitosan/glycerophosphate (CS/GP) hydrogels have physiological pH and gelation temperature optimal for the human organism (37 °C) – that is why they have been tested in various biomedical applications. However, despite this popularity, recent studies [49] suggest that the GP concentration used for rapid CS gelation (i.e., 0.4 M) is cytotoxic. Glycerophosphate may be replaced with sodium hydrogen carbonate and phosphate buffer [49]. This formulation transformed into the gel at 37 °C but had better mechanical characteristic and improved cytocompatibility.

Physical gelation can occur due to the formation of polyelectrolyte complexes between oppositely charged molecules. As it was mentioned previously, in mildly acidic conditions, chitosan is a polycation, and therefore, it can form complexes with

many polyanionic polymers and various ions. Chelation of amino groups can cause adsorption of metal cations and thus formation of complexes between chitosan and metal ions. It has been reported that ionic complexation results not only in molecular changes but also affects the structure of in situ prepared chitosan hydrogels. Nie et al. [50] studied the influence of metal ions on the hydrogel structure. Their results showed that ions with a strong affinity towards chitosan, e.g., Cu^{2+}, act as ionic crosslinking agents, increase volume shrinking tendency of the polymer, and cause transformation of the hydrogel structure from oriented fibers to multilayers. On the other hand, ions such as Ca^{2+}, that have a weak affinity with chitosan, in the presence of hydroxide ions, tend to form precipitates. Hence, inorganic particles are introduced to the polymer matrix, but the structure of the chitosan hydrogel is not affected.

Chitosan can be successfully crosslinked with tannic acid, a natural nontoxic molecule which has the ability to form ionic, hydrophobic, and hydrogen interactions with the polymer [51]. Sionkowska et al. [52] reported the influence of tannic acid crosslinking on the photochemical stability of chitosan in view of possible sterilization of chitosan biomaterial via UV irradiation. It was shown that absorption of UV light by tannic acid may affect the polymer macromolecule and lead to the scission of chitosan chains and/or crosslinking.

Bioactive chitosan hydrogels were obtained by crosslinking with laponite – platelike synthetic clay [53–55]. Dense polymer network was formed as a result of electrostatic interactions between negatively charged clay molecules and protonated amine groups of chitosan. Formation of the crosslinked structure limits the swelling behavior of the hydrogel [54]. Moreover, laponite acts not only as a crosslinker but also increases the bioactivity of the system and is a good alternative for other commonly used crosslinking agents, that are often toxic to some extent [53].

Han and Yan [56] prepared supramolecular hydrogels of chitosan and graphene oxide (GO) by changing CS/GO ratio, GO concentration, and temperature. In this system, GO worked as a two-dimensional crosslinker and the self-assembly of chitosan chains and GO nanosheets was observed due to noncovalent interactions. The hydrogel was formed at room temperature when higher amounts of GO were used and the as-prepared hydrogel exhibited self-healing properties. With lower concentrations of GO, high temperature (95 °C) treatment was necessary to obtain reversible hydrogel (Fig. 1).

3.2 Chemical Crosslinking

Permanent bonds within hydrogel network are formed via chemical crosslinking by photopolymerization, radical polymerization, enzymatic reactions, and covalent linking with, for example, aldehydes. Nature of chemical hydrogels is permanent and irreversible due to chemical processes altering molecule configuration. Chemically crosslinked chitosan hydrogels can form hybrid polymer networks (HPN), semi-interpenetrating polymer networks (semi-IPN) and interpenetrating polymer networks (IPN) [46].

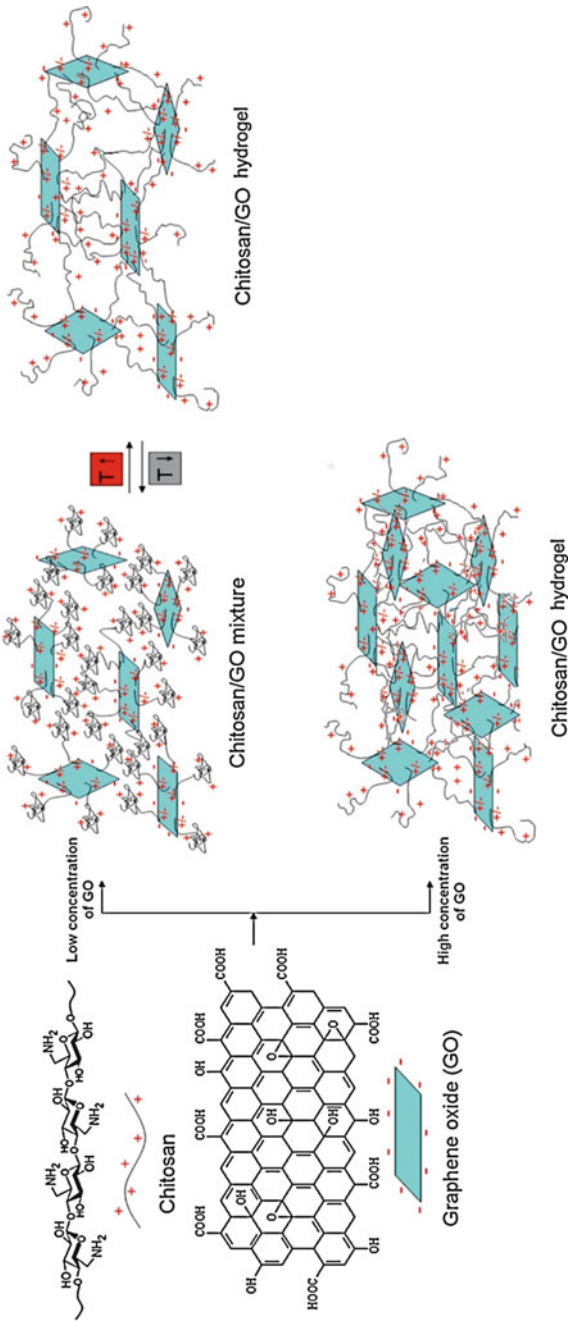

Fig. 1 Schematic mechanism for the supramolecular hydrogel formation at different conditions. (Reprinted with permission from [56]. Copyright © 2013, American Chemical Society)

Crosslinking agents used for chitosan hydrogels preparation include: glutaraldehyde (GA) [57], *N,N*-methylene-bisacrylamide (MBA) [58], glyoxal [59], and genipin [60]. At the beginning, GA gained much popularity as a crosslinker for systems where chitosan was combined with the second polymer; however, GA toxicity can impair the biocompatibility of the crosslinked polymer, and thus GA application in the biomedical field is limited. Currently, the research focus is on naturally derived crosslinkers that offer reduced or no toxicity and higher biocompatibility. One of the most popular is genipin, a compound found in the *Gardenia jasminodes Ellis* fruit. Genipin reacts promptly with chitosan and serves as a crosslinking agent even at a relatively small molar ratio. Chitosan hydrogels crosslinked with genipin are blue-colored and fluorescent [61].

Photopolymerization allows forming chemical gels by using photoinitiators and visible or UV irradiation. Photoinitiators, due to exposure to visible or UV light, produce free radicals, that induce radical polymerization and hence polymer crosslinking. The distance from light source and the duration of exposure are the main conditions controlling the reaction. Chitosan hydrogels that are photocrosslinkable have the distinct advantage of possible in situ preparation. Photopolymerizable chitosans are especially useful for fabrication of 3D scaffolds using rapid prototyping techniques. Recently, Kufelt et al. [62] fabricated N-succinyl-chitosan using succinic anhydride and then conjugated its carboxyl groups with glycidyl methacrylate (Fig. 2).

As a result, they obtained photosensitive chitosan appropriate for two-photon polymerization (2PP) processing. The 2PP method allows creating 3D micropatterning by initiating polymerization only within the laser beam focus on the photosensitive material.

In a novel approach, based on a combination of advantages of physical and chemical crosslinking, Chen et al. [63] prepared hydrogel using ethylene glycol chitosan crosslinked with a new crosslinker synthesized by reacting 1,6-diisocyanatohexan (HDI) and poly(ethylene glycol) (PEG) (Fig. 3). Only small amount of crosslinking agent was necessary to obtain semitransparent gel through the reaction between the amino and hydroxyl group of ethylene glycol CS and the crosslinker.

4 Stimuli-Responsive and Injectable Chitosan Hydrogels

4.1 Temperature Sensitive Systems

Thermosensitive hydrogels can undergo a phase transition in response to a variation of the temperature. This phenomenon is often employed when developing new biomaterial systems that should be responsive at the human body temperature. Neither parent chitin nor chitosan possesses thermosensitive properties in their native form; however, some chitosan derivatives can be designed to respond to the temperature changes. To yield thermoreversible behavior, chitosan can be grafted with poly(N-isopropylacrylamide) (PNIPAAm) [64] or poly(N-vinylcaprolactam)

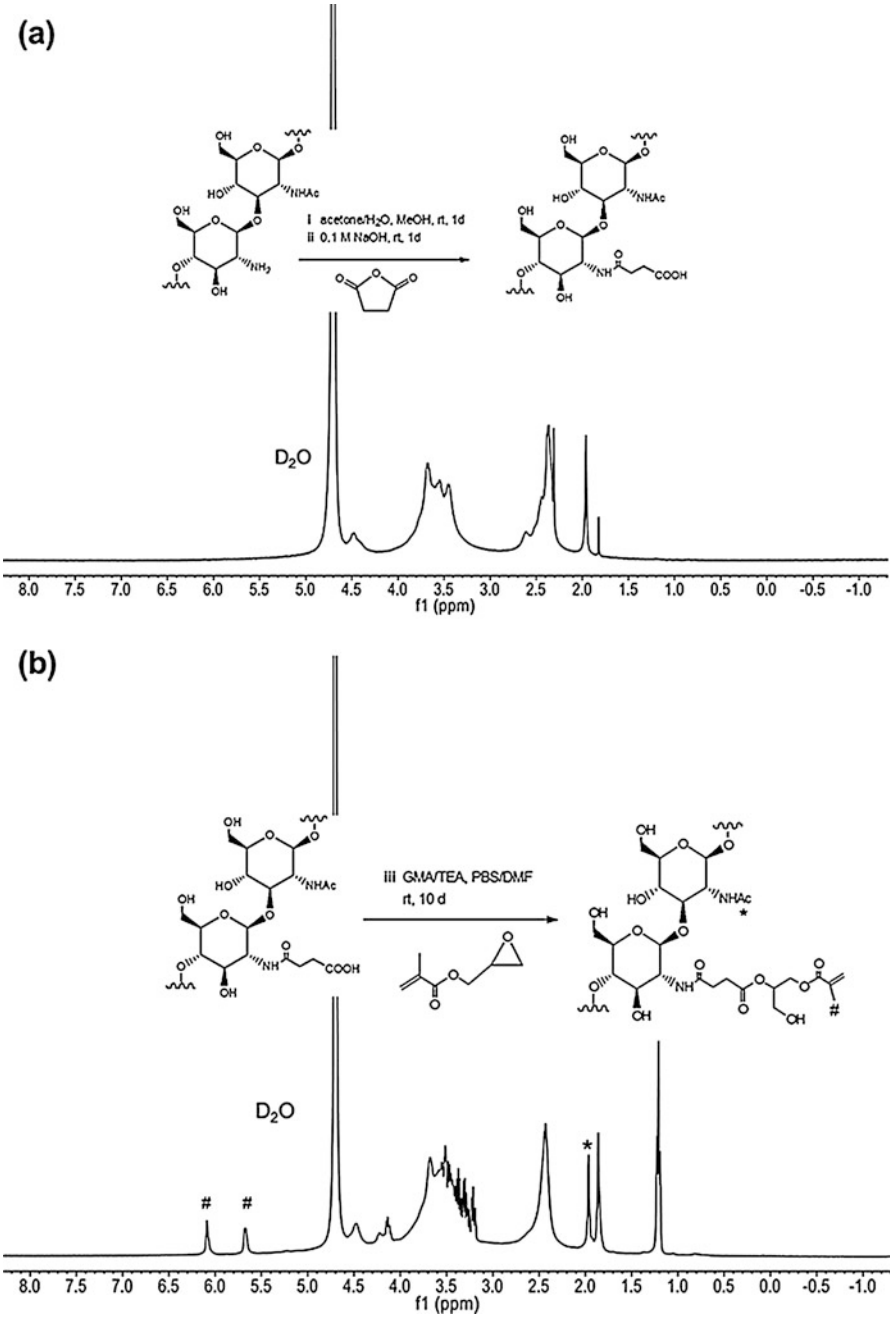

Fig. 2 1H NMR spectra in D_2O: (**a**) chitosan after N-succinylation with N-succinic anhydride (anomeric protons: d = 4.48 ppm; protons of carbohydrate backbone: 3.67–3.45 ppm; succinic $–CH_2–CH_2–$: 2.61–2.37 ppm; N-acetyl CH_3: 1.96 ppm), DS[TNBS] = 53%; (**b**) methacrylate-

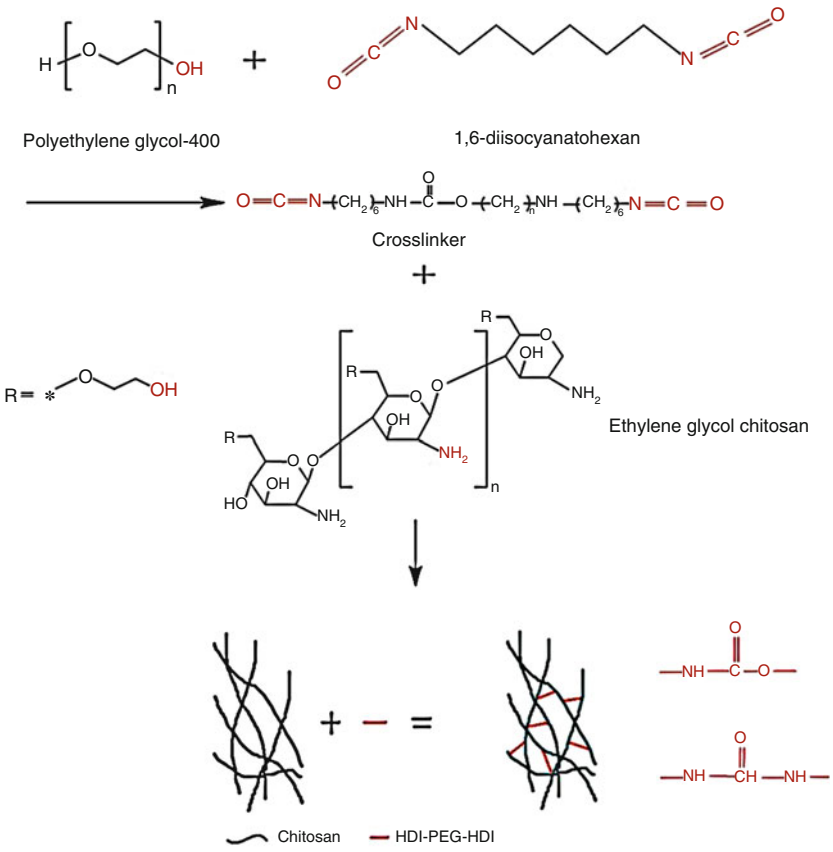

Fig. 3 A schematic drawing of the formation of the ethylene glycol chitosan hydrogel. (Reprinted with permission from [63]. Copyright © 2014, Springer Science+Business Media New York)

(PVCL) [65, 66], that both show hydrophilic to hydrophobic phase transition behavior in response to temperature increase.

Chitosan-glycerophosphate (CS-GP) system was found to be especially interesting in the biomedical field. Heat-induced chitosan gelation is triggered upon heating of the CS aqueous solution with GP added and renders physical gel around the physiological temperature. The final gelation temperature is affected by the CS degree of deacetylation and the concentration of both components. This behavior enables encapsulation of living cells or therapeutic agents within the system in its liquid state, injection in vivo and subsequent gelling at body temperature [67–69].

Fig. 2 (continued) modified chitosan (olefinic protons: d = 6.08 and 5.66; anomeric protons: 4.48 ppm, protons of carbohydrate backbone: 3.70–3.51 ppm; N-acetyl CH_3: 1.96 ppm. (Reprinted with permission from [62]. Copyright © 2015, Elsevier)

4.2 pH-Sensitive Systems

Applicable in drug delivery or bio-based adsorbents, pH-sensitive systems were obtained by graft copolymerization of N,N-diethylaminoethyl methacrylate (DEAEM) onto chitosan-tripolyphosphate (chitosan-TPP) gel beads. In acidic conditions (pH = 1), they behaved like superabsorbent gels; upon changing the pH and repeated swelling in pH = 7 and pH = 1 conditions, the chitosan-TPP-*graft*-PDEAEM beads acted as pH-responsive superabsorbent 3D matrices [34].

In another study [60], chitosan microspheres crosslinked with genipin were fabricated for removal of heparin from the bloodstream. The developed system responded to changes in pH and thus allowed to tune the rate of heparin removal. Additionally, the microspheres were cationically modified with glycidyl trimethylammonium chloride to increase heparin binding efficiency at physiological pH level (~7.4).

The pH-responsive systems can be also applied for drug delivery. Qu et al. [70] used N-caboxyethyl chitosan and dibenzaldehyde-terminated poly(ethylene glycol) to obtain hydrogels for hepatocellular carcinoma therapy. Doxorubicin release study confirmed pH-sensitivity of the developed hydrogel – due to gel degradation, the drug was released faster in the acid environment than at pH = 7.4. The higher release kinetics at lower pH (6.8 vs. 7.4) was also observed by Adeyemi et al. [71]. In their study, chitosan-based nanoparticles were loaded with bovine serum albumin, as a model protein.

4.3 Injectable Systems

Thermosensitive systems with gelation point set at a typical human body temperature are ideal candidates for application as injectable hydrogels. They can be prepared in ambient conditions and transformed into a gel after implantation. Combination of chitosan, quaternized chitosan, and α,β-glycerophosphate allowed to formulate injectable composite material (CS-HTCC/α,β-GP) that undergoes sol-gel transition at 37 °C in 3 min [68]. Additionally, CS-HTCC/α,β-GP exhibited the ability to release a drug in a controlled manner and showed antibacterial activity towards periodontal pathogens. Monette et al. [72] developed injectable hydrogels based on chitosan combined with $NaHCO_3$ and phosphate buffer. Their formulation served as an injectable scaffold for the encapsulation and localized delivery of T lymphocytes.

Wang et al. [73] prepared injectable hydrogel by introducing chitin nanowhiskers into chitosan/β-glycerophosphate disodium salt. Addition of chitin nanowhiskers significantly increased mechanical properties of the gel and reduced the gelling time at 37 °C to only 25 seconds. The nanowhiskers served as a crosslinker in the gel formation.

Application of Schiff' base reaction for the synthesis of injectable hydrogels has been reported recently [74]. Chitosan microspheres were embedded into chitosan-chondroitin sulfate hydrogel affecting properties of the composite system. Presence of solid microspheres enhanced compressive modulus of the gel, that was able to retain its structure.

5 Applications of Chitosan-Based Hydrogels

The variety of favorable properties of chitosan, such as its biocompatibility, biodegradability, antibacterial, mucoadhesive, hemostatic, analgesic, and antioxidant activity make this polysaccharide a polymer of choice in many different fields. Pharmaceutical, medical, cosmetic, or food industry – they all benefit from the use of chitosan. In the field of biomaterials, it is applied in tissue engineering, wound healing, and drug delivery systems. Due to ionic complexation described earlier, it also serves well in water purification. Some detailed examples of the application of chitosan-based hydrogels in different areas are given below.

5.1 Tissue Engineering

The rapid development of materials science and biomedicine resulted in the formation of the new field named tissue engineering (TE). Traditionally, the triad of TE consists of scaffolds, cells, and bioactive agents. The main idea behind this approach is based on regeneration of damaged tissues, rather than replacing them, by using temporary scaffold templates that degrade over time making room for a newly formed tissue. The clue here is the biocompatibility and biodegradability of the initial biomaterial support and the ability to deliver cell instructive signals. After many years of research, some basic requirements for polymeric tissue scaffolds were formulated, starting with the degradation rate matching that of regenerated tissue. TE scaffolds should be highly porous and the pore size should be fitted to a specific cell type. At the same time, this porous scaffold needs to have enough structural integrity and mechanical properties to withstand forces acting at the implantation site during the time when new tissue is formed. This includes also surgical handiness. Lastly, the scaffold has to be biocompatible and should promote cell adhesion, proliferation, migration, and differentiation, facilitating neo-tissue formation [2, 75, 76].

Chitosan, especially with high deacetylation degree, is biodegradable and biocompatible. Furthermore, chitosan hydrogels with their high water content and viscoelastic properties resemble characteristic of native tissues. Lastly, those polymer networks are easily modified to carry and release molecules influencing cell behavior. All the above features cause chitosan to be biomaterial of choice in many tissue engineering applications [77].

Grolik et al. [78] developed chitosan-based hydrogel membranes crosslinked with genipin for corneal epithelial cell cultures. The results demonstrated that especially promising properties, including favorable hydrophilicity, morphology, and mechanical characteristics, present chitosan-collagen blends that formed a homogenous mixture and both components were successfully crosslinked with genipin.

Haaparanta et al. [79] studied hybrid scaffolds in various systems: collagen/polylactide (PLA), chitosan/PLA, and collagen/chitosan/PLA for the treatment of articular cartilage defects. In another attempt [63], cartilage defect was successfully repaired with the use of ethylene glycol chitosan hydrogel. In the in vivo assay, rabbit chondrocytes cultured in the prepared hydrogel were implanted into damaged

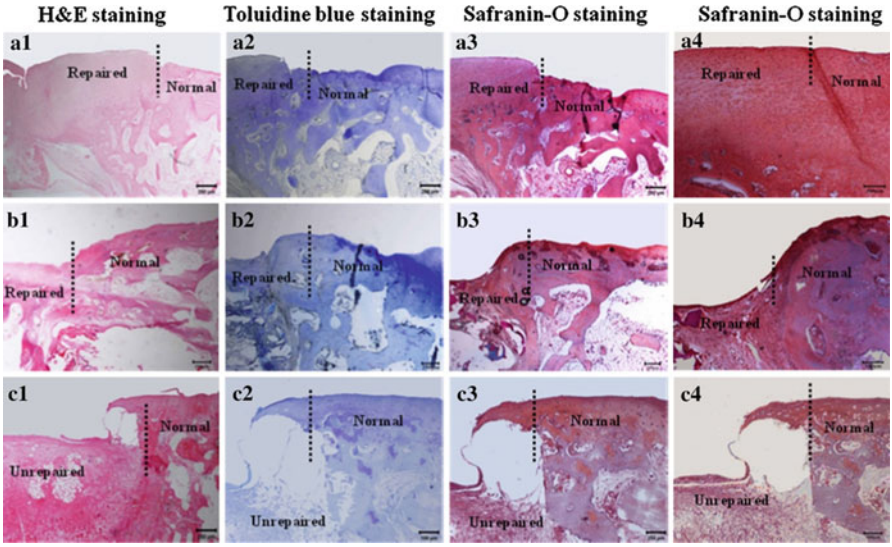

Fig. 4 Repair of cartilage defects in vivo. Ethylene glycol chitosan-chondrocytes repair rabbit knee joint defects at 12 weeks. (**a**) Experiment group; (**b**) Blank group (ethylene glycol chitosan hydrogel scaffold without chondrocytes); (**c**) Control group; 1–3 scale bar 250 μm, 4 scale bar 100 μm. (Reprinted with permission from [63]. Copyright © 2014, Springer Science+Business Media New York)

knee joint. Over the period of 12 weeks, chitosan hydrogel degraded and the defect was filled with cartilage-like tissue (Fig. 4).

Similarly to other polymers, chitosan has relatively weak mechanical properties, hence for successful application in bone TE, it needs to be combined with other materials, usually with bioactive ceramics, for improved mechanical and biological performance. Dan et al. [80] fabricated chitosan-gelatin-nanohydroxyapatite (nHAp) composite scaffold with a mean pore size of 100–180 μm, showing improved attachment and growth of the MC3T3-E1 cells due to the presence of nHAp. Qiao et al. [81] reported research toward developing self-sterilized bone TE scaffold in three steps: crosslinking of chitosan with genipin, freeze-drying of the construct, and biomineralization of nHAp layer. To improve antibacterial properties silver ions were introduced via in situ synthesis of silver phosphates in the HAp nanostructure by substitution of calcium ions. Using the technique of high compression, Kucharska et al. [82] fabricated microsphere-based scaffolds composed of chitosan and tri-calcium phosphate (TCP) (Fig. 5).

5.1.1 Design and Construction of Three-Dimensional Chitosan Scaffolds

All native tissues are three-dimensional (3D) complex structures, hence cells prefer 3D scaffolds over 2D surfaces. 3D scaffolds resemble the architecture of the native extracellular matrix, providing an appropriate environment for cell growth and

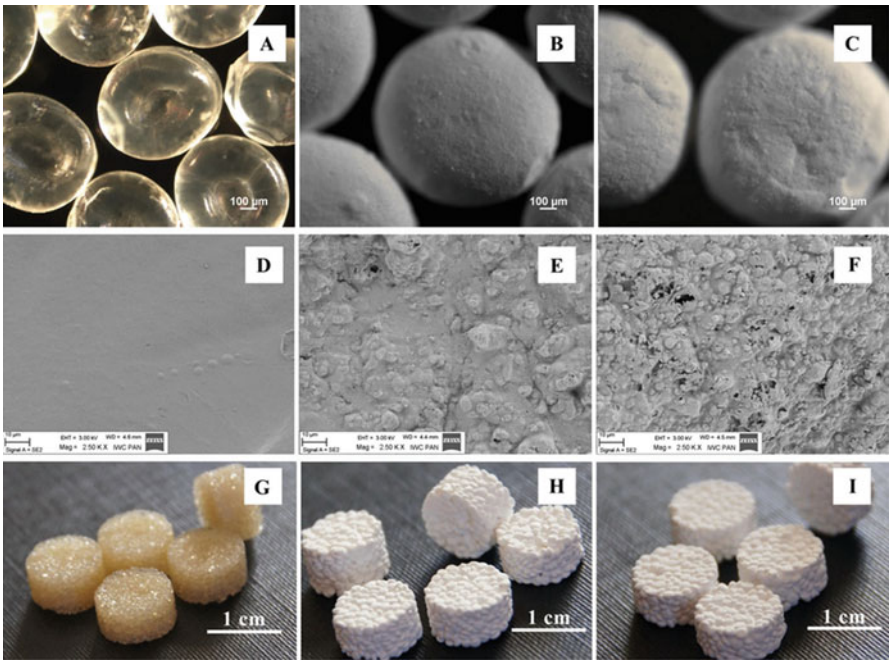

Fig. 5 Photographs of CH, CH_5TCP, and CH_10TCP microspheres, respectively, from the left-hand side. (**a**–**c**) Optical microscope, ×5 magnification; (**d**–**f**) SEM analysis of granules microstructure, magnification ×2500; (**g**–**i**) The digital photographs of formed CH and CH/TCP scaffolds. (Reprinted with permission from [82]. Copyright © 2015, Springer Science+Business Media New York)

proliferation. There is a growing interest in various fabrication methods that allow obtaining 3D morphologies. Those methods include electrospinning, phase-separation, self-assembly, freeze-drying, and 3D printing [83].

Electrospinning technique allows forming continuous nanoscale or microscale fibers from the polymer solution, in the presence of the electric field [84, 85]. The polyelectrolyte nature of the chitosan dissolved in acidic media complicates the process, as protonated amine groups of the chitosan backbone start to repulse each other when the high voltage is applied. One of the first successful preparations of electrospun chitosan mats using trifluoroacetic acid (TFA) as a solvent was reported by Ohkawa and coworkers [86]. Chitosan amino groups formed salts with TFA, thus eliminating the problem of ionic interactions and facilitating the spinning process. Chitosan nanofibrous mats were also fabricated using TFA-dichloromethane and concentrated acetic acid.

Freeze-dried scaffolds are formed by freezing of the polymer solution and then removal of the frozen solvent crystals by direct sublimation under vacuum, leaving empty spaces – pores. In the freeze-drying process, scaffold architecture may be tuned by changing the solvent and polymer type, the polymer solution concentration, and the freezing conditions [84, 87]. The morphology and the pore size of chitosan

scaffold are affected by the freezing temperature. When samples were frozen at lower temperatures, the cooling rate was faster and the ice crystals had less time to grow – resulting pores were smaller, but their amount was higher. On the other hand, when the cooling rate was slower (lower freezing temperature), crystals had time to grow yielding a lower number of bigger pores [87]. In the work of Kavitha Sankar, Rajmohan, and Rosemary [88], freeze-drying was used to obtain chitosan sponge with blood absorbing capacity suitable for hemostasis. Freeze-drying can be also applied to the fabrication of chitosan-based composite scaffolds. Mohammadi et al. [89] prepared freeze-dried chitosan scaffolds reinforced with multiphasic calcium phosphate short fibers that exhibited enhanced mechanical and biological properties.

One of the latest technologies in scaffold fabrication is 3D printing [90]. However, when it comes to hydrogels, it is also especially challenging. Precise, layer-by-layer deposition of hydrogels is difficult due to their usually weak mechanical properties causing deformation of the scaffold architecture as the hydrogel struts tend to collapse under the weight of subsequent layers [91]. Many attempts were made to overcome this problem, mainly by using in situ gelling method. This way, the 3D printed shape was retained, but the chemicals used for gelation increased the risk of cytotoxicity. An alternative approach was proposed by Wu et al. [92]. The chitosan-based printable ink was prepared in a mixture of acetic, lactic, and citric acid and printed directly in air, in ambient conditions. Relatively, high chitosan concentration combined with the printing of very thin struts enabled partial hardening of the struts by solvent evaporation. Then, the scaffolds were physically crosslinked by neutralization in sodium hydroxide solution. As a result, the authors obtained highly flexible chitosan scaffolds with precisely controlled architecture for guided cell growth (Fig. 6).

In the 3D bioprinting technology, living cells can be incorporated into hydrogel matrix and fabricated into bioscaffold with precisely controlled architecture. In one of the recent studies [93], gelatin/sodium alginate/carboxymethyl chitosan (Gel/SA/CMCS) was combined with bone mesenchymal stem cells (BMSC). Resulting 3D hydrogel scaffold exhibited homogenous cell distribution, good mechanical properties, antibacterial activity, and favorable degradation rate. BMSCs loaded into this complex polymer matrix showed high viability.

5.2 Wound Healing

Each year, many people suffer from skin wounds, e.g., skin lesions or burns. This common health problem can have serious consequences as skin serves as a barrier protecting the organism from many harmful factors, like, e.g., bacteria. Hence, it is important to provide appropriate conditions for wound healing and thus recreating damaged protective layer – the skin. Wound healing process consists of four phases, i.e. hemostasis, inflammation, proliferation, and remodeling [94]. Chitosans with their high swelling ability, wound healing, antibacterial, hemostatic, and analgesic properties earned considerable interest as a wound management material.

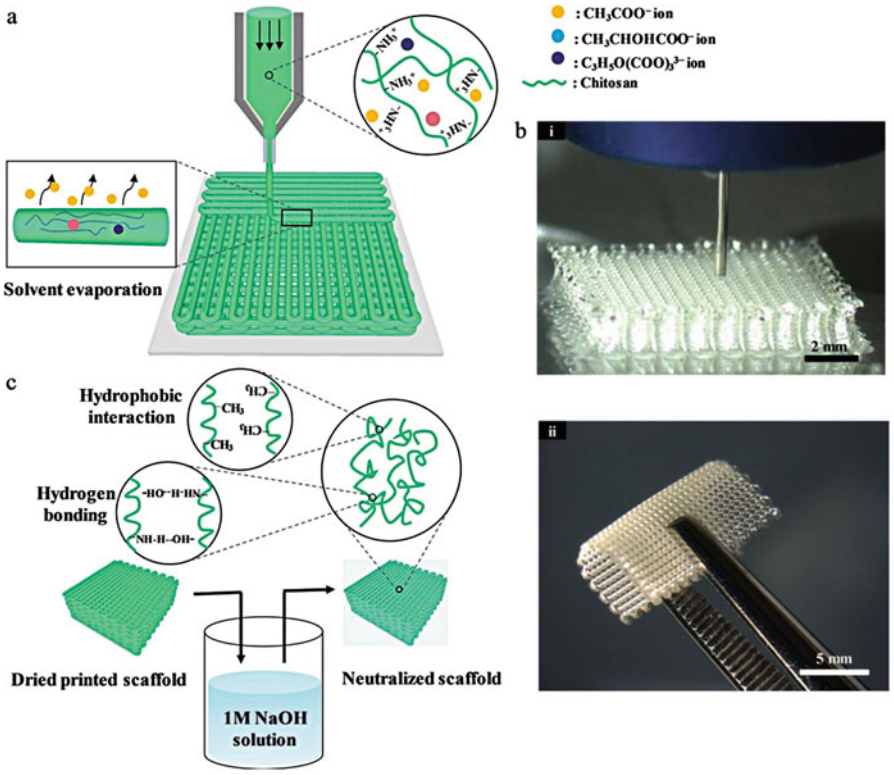

Fig. 6 (**a**) Schematic representation of 3D printing of a chitosan ink prepared using an acidic mixture and partially hardened via solvent evaporation. (**b**) (i) Optical image of the printing of a 30-layer 3D chitosan scaffold through a 100 μm micronozzle and (ii) optical image of a 10-layer chitosan scaffold fabricated with a 100 μm micronozzle and folded using a tweezer. (**c**) Schematic illustration of the neutralization step for yielding physical gelation with hydrophobic interaction and hydrogen bonds to form a chitosan hydrogel scaffold. (Reprinted with permission from [92]. Copyright © 2017, WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim)

Huang et al. [95] used scalded rats model to investigate analgesic and wound healing effect of chitosan and carboxymethyl chitosan. The results confirmed that both, CS and CMCS, promote wound healing; however, analgesis was only observed in the case of CMCS. In another study [96], low molar mass O-CMCS was reacted with furfuryl glycidyl ether, creating the furan-coupled O-CMCS (VLC-chitosan). Next, bovine serum albumin (BSA) was encapsulated in the polymer matrix by crosslinking of VLC-chitosan in the presence of Rose Bengal under visible light irradiation. In vivo animal assay demonstrated that VLC-chitosan containing murine epidermal growth factor (mEGF) reduced inflammation and sustained epithelial regeneration and fibrosis.

Chitosan oligosaccharides have anti-inflammatory, immunostimulating, and antioxidant properties. Thus, they are able to accelerate wound healing, what was

recently confirmed by Sandri et al. [97]. In the tested system, chitosan oligosaccharide was combined with a clay mineral, halloysite nanotubes (HNTs). Resulting nanocomposite material proved to be biocompatible with human dermal fibroblasts. Moreover, after 18 days of in vivo assay using murine model, full recovery of skin structure was observed.

5.3 Drug Delivery

Controlled drug delivery systems (DDSs) allow to overcome drawbacks of traditional, systemic administration of various therapeutics, i.e., low bioavailability of the active agent, and the unnecessary exposure of the whole organism to the drug, while its activity is usually needed only locally. DDSs have the ability not only to deliver therapeutic molecules to the specific location but also to release them in a controlled manner within the predefined time frame. Different types of materials were tested as possible drug delivery systems, with special attention paid to hydrogels, and among them chitosan-based ones.

As it was mentioned previously, crosslinking affects the swelling behavior of the hydrogels and consequently alters the drug diffusion characteristic. Slower drug release was observed in the case of chitosan-laponite (CS-LP) system when compared to pure CS due to strong ionic interactions between positively charged NH_3^+ groups of the chitosan chain and negatively charged laponite particles [54]. Dense, crosslinked polymer network is less prone to water absorption and swelling, preventing rapid dissolution of the drug entrapped within the network.

Sustained drug release system for wound dressing material was developed by Murthy et al. [98] by impregnating ciprofloxacin-loaded chitosan microparticles (CSMP) into the chitosan (CS-CSMP) or poly(vinyl alcohol) (PVA-CSMP) scaffolds. The high swelling ability of CS-CSMP scaffolds allowed to reach 82% of drug release. Both in vitro studies with NIH 3 T3 fibroblasts and HaCaT human keratinocytes confirmed biocompatibility of the scaffolds.

Cihan et al. [99] developed well-defined, spherical, hollow chitosan nanoparticles (size range: 30–300 nm) for the controlled delivery of highly lipophilic drug (Probucol). It was possible by first dissolving the drug in the hydrophobic core of the micelles of Pluronic copolymer through ionic gelation and crosslinking of chitosan around the micelles. Results showed very high drug uptake (up to 93.4%) and pH-sensitive behavior of the nanoparticles – significant increase of the drug release was observed at the slightly acidic pH (~6.8) when compared to pH 7.4. Ionic gelation (with TPP) was also incorporated for preparation of DDS based on N-succinyl-chitosan (SCS), N-glutaryl-chitosan (GCS), and taxanes [100]. Drug-loaded SCS and NCS spherical particles had a diameter of 300–350 nm and more than 50% of the drug releasing efficiency. Cytotoxicity of the taxane-containing nanoparticles against cancer cells was confirmed.

More complex, smart system was developed by Cui et al. [101]. Folic acid (FA) functionalized thiolated chitosan was used to fabricate multistimuli responsive microcapsules (MCRS-CS-MCs) via the sonochemical method. The obtained MCR-

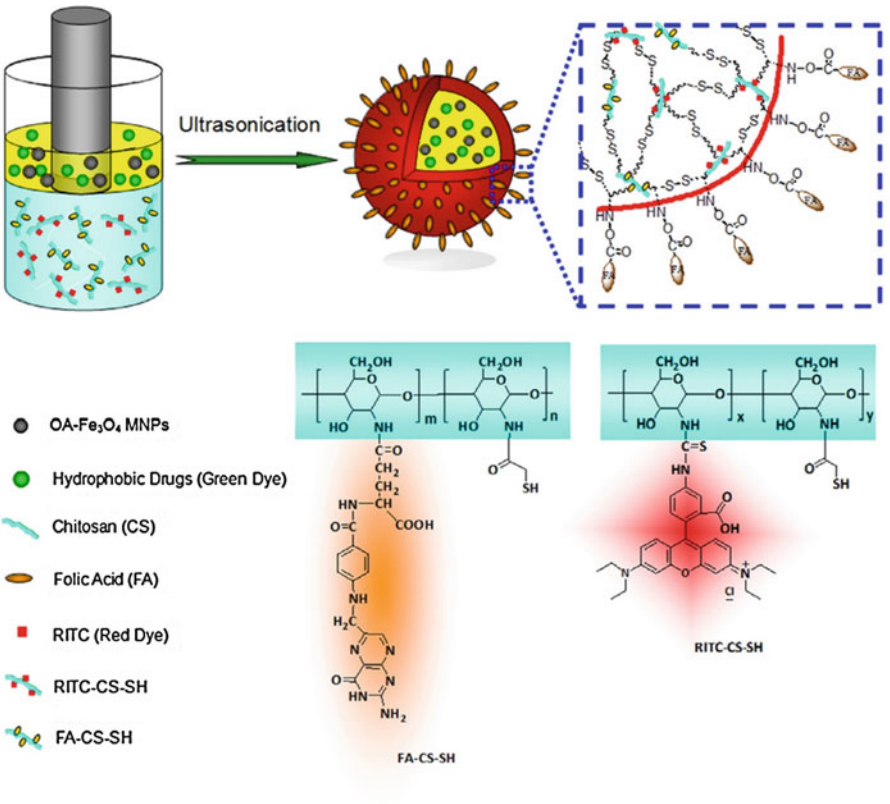

Fig. 7 The sonochemical synthesis schematic of multistimuli responsive smart chitosan-based microcapsules (MSRS-CS-MCs). (Reprinted with permission from [101]. Copyright © 2017, Elsevier)

CS-MCs spherical particles were loaded with oleic acid (OA) modified Fe_3O_4 magnetic nanoparticles and a green fluorescent dye, while FA and red fluorescent dye were immobilized onto the microcapsule shell (Fig. 7).

5.4 Water Purification

Water purification is currently an emerging problem worldwide. Industrial wastewaters are usually contaminated with organic and inorganic substances, such as heavy metal ions, pesticides, dyes, various microorganisms, and solid particles. Many of those can be removed using natural adsorbent systems. Chitosan, thanks to the presence of free amino groups, can serve as an effective adsorbent and coagulant, reducing the amount of suspended solids, chelating metal ions, or binding dyes.

Superhydrophobic and superoleophylic chitosan sponge was developed via TPP/citral crosslinking and octadecanethiol modification for the removal of oils from water in environmental remediation [102]. The CS sponge was able to absorb the amount of oil equal up to 60 times of its own weight and remained high absorptive capacity after many cycles. It was proposed that the oil or organic solvents were absorbed by the sponge due to hydrophobic interactions between them and the sponge and the capillary pore effect. Tested absorptive capacity included, e.g., hexadecane, toluene, chloroform, hexane, dichloromethane, pump oil, soybean oil and silicone oil. Combined with a peristaltic pump, the sponge allowed for continuous oil-water separation.

Chitosan may be also applied as a carrier for photocatalyst and photosensitizers immobilization for the visible-light-driven photodegradation of aqueous pollutants. Gmurek et al. [103] investigated the application of photosensitive phthalocyanine-immobilized chitosan as a structure generating singlet oxygen ($^1O_2$). The results confirmed its applicability with natural sunlight and effective water pollutant removal. Moreover, photoactive chitosan did not lose their photosensitizing properties even after several cycles.

Ampholytic chitosan/carrageenan (CS/CRG) microspheres exhibited high adsorption capacity towards cationic and anionic dyes and heavy metal ions. The microspheres adsorbed water contaminants efficiently due to their strong electrostatic and chelating affinity. Additionally, they were modified with Fe_3O_4 nanoparticles to allow magnetic separation. Developed microspheres are environmentally friendly since they can be easily recycled, reused and biodegraded in soil [104].

5.5 Other Applications

Chitosan is often applied as a coating material to improve cell compatibility of the substrate material and add functional groups on the surface that enable further modifications. In a recent study by Douglas et al. [105], chitosan was deposited on the titanium surface and subsequently modified with polyphenol-rich plant extracts. Chitosan coating improved cell adhesion, enhancing biological properties of the Ti. In another study [106], chitosan was covalently immobilized onto Ti surface to reduce the risk of implant-related infection by preventing bacterial colonization and enhance implant osseointegration.

6 Conclusions

Chitosan, a derivative of one of the most widespread natural polymer – chitin, gets an increasing attention both in academic and applied research due to its favorable properties. Chemical structure of chitosan allows various controlled specific modifications that is one of the most important advantages of this polymer over other polysaccharides like starch or galactomannans. Moreover, it is nontoxic, antibacterial, biodegradable, and biocompatible that makes chitosan very attractive

material in the biomedical field. Chitosan, with its outstanding properties, is one of the most promising and recently studied bio-based polymers for drug delivery, tissue engineering, gene therapy, and other medical applications. Hence, in this chapter, we present the state of art in the area of chitosan-based hydrogels – their preparation, properties, and application directions.

Chitosan is also an attractive material to further develop "green" chemistry strategies, including liquid solvents, wastewater treatment, heavy metal chelation, and biosensing. The results obtained so far show that there is still room for structural and morphological modification of chitosan to design novel chitosan-based hydrogels with enhanced properties. For instance, one of the latest technologies in scaffold fabrication is 3D printing, which for hydrogels is quite challenging; precise, layer-by-layer deposition performed easily for thermoplastic matrices is hard to achieve for hydrogels because of deformations occurring due to their weak mechanical properties. Nanostructural modifications may help to offer better solutions toward innovative hydrogel 3D printing approaches in biomedicine.

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Chitosan-Based Polyelectrolyte Complex Hydrogels for Biomedical Applications

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Abstract

Chitosan is produced by deacetylation of chitin, a structural element in the exoskeleton of crustaceans and insects, which is the second most abundant natural biopolymer after cellulose. Chitosan has found applications in many primary industries such as: agriculture, paper, textiles, pharmacology, cosmetology, and wastewater treatment. There is a major interest in using chitosan for biomedical applications due to its generous properties including biocompatibility, low toxicity, hemostatic potential, good film-forming character, anti-infectional activity, and susceptibility to enzymatic degradation. The property of chitosan which will be in detail discussed in this chapter refers to its ability to form polyelectrolyte complexes due to the presence of amine groups in its repetitive unit. Therefore, chitosan in aqueous acid solution reacted with anionic polysaccharides such as: carboxymethylcellulose, xanthan, alginate, carrageenan, gellan, oxychitin and oxypullulan, chondroitin and hyaluronan, poly(galacturonic acid), poly(L-glutamic acid) as well as synthetic polyanions such as poly(acrylic acid) to give polyelectrolyte complexes. One major advantage of polyelectrolyte complexes for biomedical use is their superior biocompatibility in respect with other formulations which are using synthetic crosslinkers to obtain stable hydrogels. The aim of this chapter is to describe the process of chitosan complexation with other natural and synthetic polyanions, the factors that influence the formation and stability of these polyelectrolyte complexes and the potential applications in biomedical field.

Keywords

Polyelectrolyte complexes · Hydrogel · Chitosan · Synthetic polyanions · Natural polyanions · Complexation · Biomedical applications

1 Introduction

Polyelectrolyte complexes (PEC) are a group of materials that belong to the broad class of interpolymer complexes (IPC). They are formed by mixing two or more polymers capable of interacting with each other into solution. The interactions that contribute to IPC formation can be hydrogen bonding, van der Waal's forces, ionic and covalent bonds, depending on the chemical structure, the conformation of the polymer chains, and the conditions for the preparation of the polymer mixture (the nature of the solvent [1, 2], pH, ionic strength, temperature [3], concentration of solutions, and the mixing ratio).

The mechanism of the polyelectrolyte complexes (PECs) formation has been extensively studied by Kabanov et al. [4–7].

The stability of PECs is influenced by the nature and polarity of polymers, their degree of polymerization, and the pH of the reaction medium [8]. PECs are an important source of materials whose properties can be tailored depending on the desired characteristics or on the field in which they will be used. Various polymers

represent an important source of raw materials for PECs preparation, but the chitosan occupies a privileged place in the polymer world due to its abundance in nature and also to the presence of many amine groups capable to form the quaternary ammonium groups, turning it into the polycationic component of the polyelectrolyte complex. Importantly, in this form chitosan becomes soluble in water, allowing electrostatic interactions with water-soluble polyanions.

2 Polyelectrolyte Complexes with a Hydrogel Character

Polyelectrolyte complexes with a hydrogel character – polyelectrolyte hydrogels (PEHs) – have lately attracted attention due to their ability to respond to external chemical or physical stimuli (pH, ionic strength, solvent polarity, external electric field [9, 10]) being also known as "smart hydrogels."

PEHs are three-dimensional networks formed through the electrostatic interactions of polyelectrolytes of opposite charges when ionic forces cross-link polymers forming a network. Ionic crosslinking is reversible; at high ionic strength, the polyelectrolyte complex decomposes slowly. This behavior is advantageous because hydrogels of this type are more biodegradable than hydrogels formed by covalent cross-linking [11, 12].

Due to the fact that PEHs have physical properties similar to biological tissues, they are increasingly used for the development of controlled drug delivery systems or matrices for tissue engineering. Poor cross-linking cause poor mechanical properties in the swollen state, leading to a limitation of the practical applications. Nowadays, researchers are trying to solve this problem by various methods, such as PEH grafting on the surface of a solid support or the development of the polyampholyte gels with the supramolecular structure that determine the retention of a lower amount of water as well as to induce a higher stiffness and fatigue resistance of gels [13]. This latter type of PEH is formed from macromolecular compounds containing both positive and negative charge substituents on the same chain, their final properties being completely different from the starting polymers [14].

The PEH classification as well as the general classification of PECs takes into account the nature of the polyelectrolytes involved in complexation. Based on this, PEHs are divided into three major groups:

- *PEH formed between synthetic polymers*. PEH resulting from the ionic interaction between poly(vinylbenzyltrimethyl-ammonium chloride) and poly (methacrylic acid) is a typical example. It was found that the complexation efficiency is maximal when the stoichiometry of polycation and polyanion ions is practically achieved.
- *PEH formed between synthetic polymers and natural polymers*. Most examples include combinations obtained by the interaction of synthetic polymers with proteins [poly(acrylic acid) with lysozymes, poly(dimethyldiallyl ammonium chloride) with bovine serum albumin and others].

– *PEH formed between natural polymers*, especially chitosan with natural polyanions [alginic acid, carrageenan, xanthan, pectin, proteins] or their derivatives [carboxymethyl cellulose, carboxymethyl dextran, dextran sulfate]. In this case also, the major factors of complexation are the concentration and ratio of the partners, the ionic strength, the pH of the solution and others.

Therefore, the formation of PEC, in particular of PEH takes place at the contact of polyacids and polybases in aqueous solutions or between the metal salts of polyacids and the quaternary ammonium salts of the polybases with the release of the low molecular counterions. In addition to electrostatic interactions, hydrogen bonds, ion-dipol interactions, or hydrophobic interactions can play an important role. It is known from literature that PEC formation is an endothermic process [15]. The formed system can either remain in solution or separate into a dilute phase and a complex coacervate phase, or separate into a more or less compact precipitate or a hydrogel – which is the most interesting case for PEH formation.

3 Polyelectrolyte Complex Hydrogels of Chitosan

Particular attention is paid to a natural cationic polysaccharide namely chitosan, which is the second most abundant natural biopolymer after cellulose. The presence of many amine groups as a substituent on the backbone chain capable of protonation in a weakly acidic environment makes it a weak polybase that can be used in the formation of biocompatible PEHs. Due to the semicrystalline structure of chitin and to the process of partial deacetylation, chitosan is characterized by a heterogeneous composition represented by the formula shown in Fig. 1.

It is a statistical copolymer of β-[1,4]-linked 2-acetamido-2-deoxy-D-glucopyranose and 2-amino-2-deoxy-D-glucopyranose [16]. Its physical and chemical properties highly depend on the degree of deacetylation.

The ionic reaction between the quaternized amine groups of chitosan and the oppositely charged groups of a polyanion is the main interaction that results in PEC formation. The strength of these interactions is far superior to the van der Waal's secondary forces that occur at the solution contact between chitosan and a nonionic polymer within solution [e.g., poly(vinyl alcohol)]. In addition to ionic bonds,

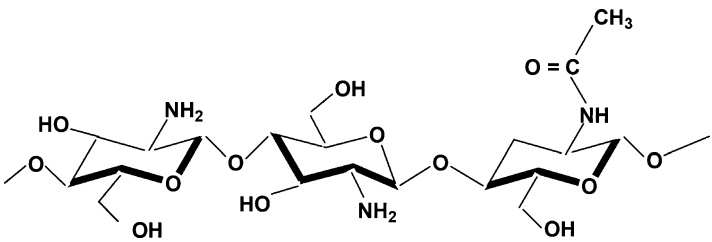


Fig. 1 The structural formula of chitosan

secondary interactions such as hydrogen bonds and amide bonds between chitosan and the polyanion partner may also occur.

The resulting network lies in a hydrophilic microenvironment containing large amounts of water. This gives a product with important hydrogel properties.

An important characteristic of hydrogels and in particular of PEHs is their ability to swell in water. It is determined essentially by cross-linking density of the network and by the degree of interaction of the two polyions, so that this characteristic can be modeled by controlling the ionic cross-linking reaction. The cross-linking density depends on global charge densities of the ionic partners. When the charge density of a polymer is lower, the proportion in the PEH becomes higher due to the fact that more interactions between the polymer chains are required [17].

The advantages of PEC preparation consist in the fact that the reaction takes place:

- Without adding other substances as catalysts, initiators and chemical crosslinking agents.
- In aqueous solution, thus maintaining the biocompatibility and reducing the toxicity and undesirable side effects. In this case, injectable solutions can be obtained, which present sol/gel transitions when they are injected into the body, thus having the possibility of regenerating the affected tissue.

However, gels based on PEC also have a number of drawbacks such as the pore size is difficult to control, they have a limited mechanical strength and due to the fact that the ionic bonds can unfold, an uncontrolled decomposition of these gels can take place [18].

The most important factor that controls the reaction of ionic cross-linking influencing the cross-linking density and even the porosity of the formed hydrogel is the pH of the solution. The reaction occurs at pH values near the pKa range in which the two polymers have opposite charges.

Other factors which can influence the PEC preparation are: the temperature, the ionic strength, the mixing order, the polymer flexibility, the molecular mass and the degree of acetylation of CH, the degree of substitution of the other polyelectrolyte, the nature of the solvent, the distribution of charges along the polymer chain, the ratio between the two components, the time of interaction, the nature and position of the ionic groups on the macromolecular chains [19–27].

PECs based on CH are systems very well tolerated by the organism [28, 29], and for this reason, this chapter highlights the importance and current achievements in the field of biomedical applications of polyelectrolyte complex hydrogels based on chitosan.

Nowadays the technologies offer the possibility of synthesizing PECs in various forms of presentation as shown in Fig. 2.

3.1 Polyelectrolyte Complex Hydrogels Based on Chitosan and Synthetic Polyanions

As mentioned above, the electrostatic attraction between the cationic group of the chitosan and an anionic group from another polyelectrolyte is the main interaction

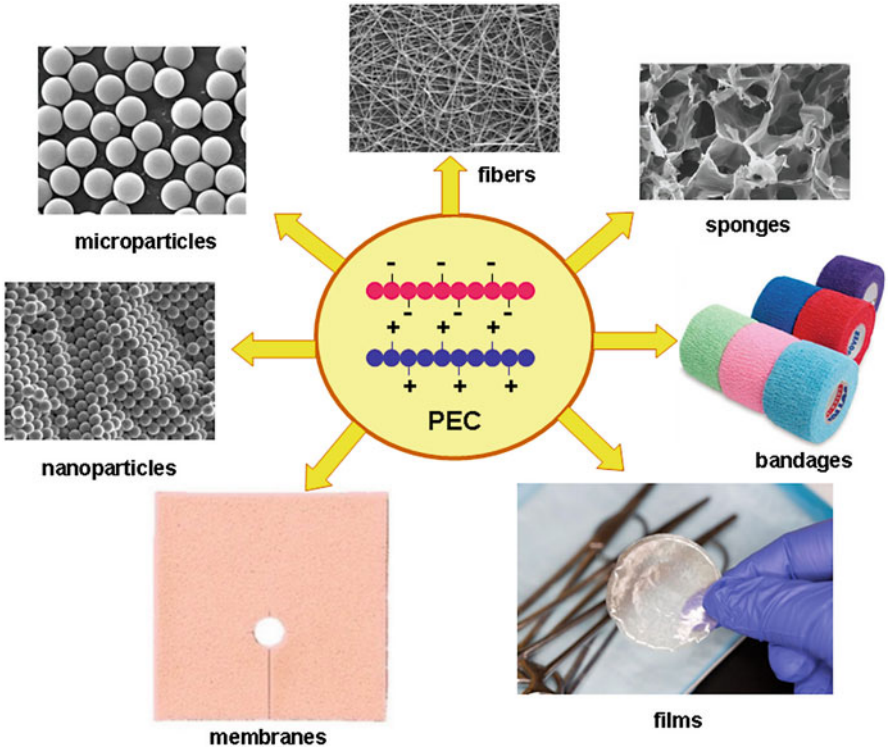


Fig. 2 Types of polyelectrolyte complexes based on chitosan

which leads to the formation of the polyelectrolyte complexes [30]. Synthetic polyanions which form PEC with chitosan are presented in Fig. 3.

3.1.1 Chitosan–Poly(carboxybetaines) Polyelectrolyte Complexes

Although polybetaines are not polyelectrolytes, they are synthetic ionic polymers which can form complexes by means of ionic interactions with CH. According to the nature of the anionic group, polybetaines can be: poly(carboxybetaines), poly (sulfobetaines), and poly(phosphobetaines).

Thus, new interpolymeric complexes have been obtained, using as partners two poly(carboxybetaines) with structural units of [1-vinyl-3-(1-carboxymethyleneimidazolium) betaine] (PNVIBL-1) and [1-vinyl-3-(2-carboxyethyleneimidazolium) betaine] (PNVIBL-2).

A careful analysis of literature data shows that usually, the polybetaines are obtained by two ways:

- Betainization of acrylic or vinylic monomer which contains a tertiary amine group followed by the (co)polymerization of the betaine monomer [31]
- Betainization of a polymer which contains a tertiary amine group, named precursor, by means of corresponding polymer-analogous reactions [32, 33]

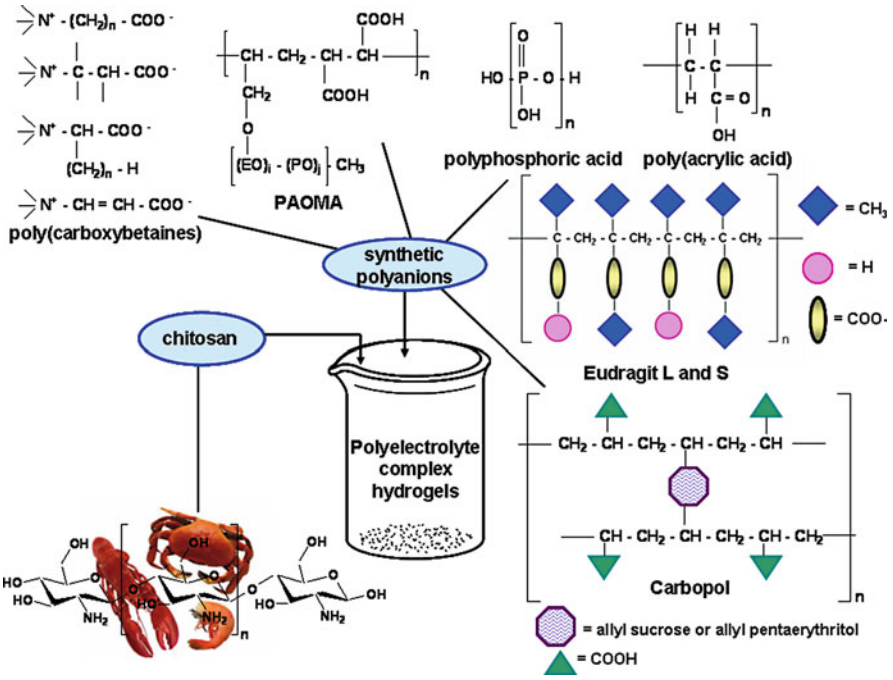


Fig. 3 Type of synthetic polyanions which form PEC with chitosan

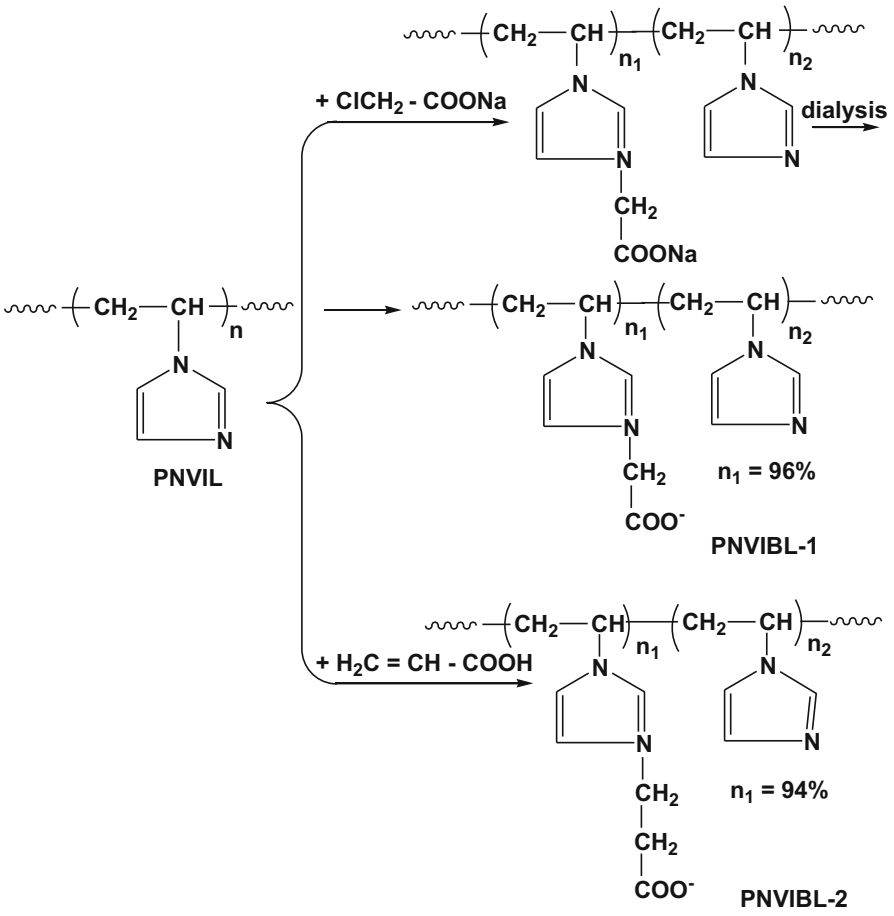
It can be stated that betainization is based on the alkylation reaction of tertiary amines but involving the alkylation agents with special structure. The difference between the two types of reactions consists, however, in the fact that alkylation leads to the appearance of the compounds with quaternary ammonium groups, while the betainization results in the formation of compounds which contain both anionic and quaternary ammonium groups.

The poly(carboxybetaines) mentioned above have been obtained by the quaternization of poly(N-vinylimidazolium) (PNVIL) with sodium monochloracetate [34] and respectively by the nucleophilic addition reaction of PNVIL to carbon–carbon double bond from acrylic acid [35] as it is presented in Scheme 1.

A synthetic polymer must satisfy a very important condition, which is nontoxic when it is used to obtain the macromolecular supports for the retention of biologically active compounds (drugs and enzymes). For this purpose, toxicity tests have been performed on poly(carboxybetaines) and their precursor PNVIL.

The toxicity studies have been carried out on homogenous groups of ten white SWISS laboratory mice, the polymer doses being administered in two ways: intraperitoneally and orally (per os). These studies revealed the following aspects:

- The death of the animals within a range of 1–14 days after the administration of the polymer dose
- Animal behavior during the study after the administration of the polymer dose



Scheme 1 Synthesis routes of poly(carboxybetaines)

– The anatomical and pathological examination of the samples collected from the liver, kidneys, lungs, heart, and peritoneum of all the deceased animals as well as from the surviving animals which were randomly sacrificed at the end of the observation period

All experiments were performed in accordance with Directive 2010/63/EU of European Parliament and Council on the protection of animals used for scientific and experimental purposes.

Following the study, we have estimated that the LD_{50} (the lethal dose which killed 50% of the test animals) for the PNVIL is situated around 450 mg/kgc, but in case of PNVIBL-2 polymer, we consider the maximum dose used as MTD (maximum tolerated dose). Also, we found that PNVIBL-1 presents antimicrobial activity against Escherichia coli [36].

In order to obtain the complex microparticles (type C), it was used PNVIBL-1, PNVIBL-2, chitosan, and two variants of the complex coacervation method.

First variant – A slightly acidic solution obtained by dissolving chitosan and polybetaines (molar ratio 1:1) in 0.1 N acetic acid, and 0.1 N hydrochloric acid was added dropwise to a 1 N Na_2CO_3 solution. The interaction between two oppositely charged polymers is affected by the pH of the solution because of changing of the dissociation degree. After Kubota, the forming mechanism of the ionic bonds between chitosan and poly(acrylic acid) depends on the pH of the solution (Scheme 2) [37, 38].

A similar mechanism to that used by Kubota at pH = 3 can be proposed for microparticles C in the first phase of the first variant (Scheme 3).

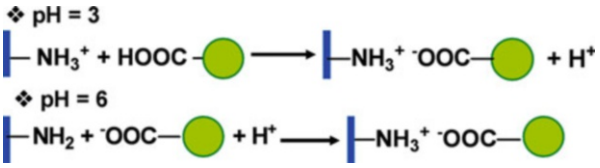
Second variant – The slightly acidic solution of the chitosan was added dropwise to the solutions of poly(carboxybetaines) obtained by dissolving PNVIBL-1 and PNVIBL-2 in 1 N Na_2CO_3, varying different parameters such as: temperature, molar ratio between CH and the two poly(carboxybetaines), and the synthesis reaction time. In the case of the second variant, it is possible that the complex formation can be obtained as follows:

1. By means of electrostatic interactions, as soon as the chitosan solution has come into contact with the poly(carboxybetaine) solution
2. By means of chitosan precipitation in the reaction medium due to the presence of 1 N Na_2CO_3, which is a nonsolvent for this type of polymer, followed by the penetration of the polybetaines into the matrix of the microparticles, by a diffusion process

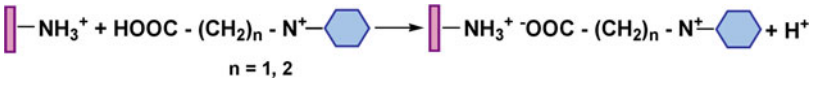
The reaction between polybetaines and chitosan can be presented schematically as in Fig. 4.

The preparation conditions for C microparticles are presented in Table 1 and Table 2.

Taking into consideration, the presence in the FT-IR spectra of complex microparticles of the absorption bands characteristic to COO^- and NH_3^+, we can assert that the hydrogel polyelectrolyte complex can be obtained mainly by means of ionic



Scheme 2 The mechanism for preparation of PEC based on chitosan and poly(acrylic acid)



Scheme 3 The mechanism of C microparticles preparation at pH = 3

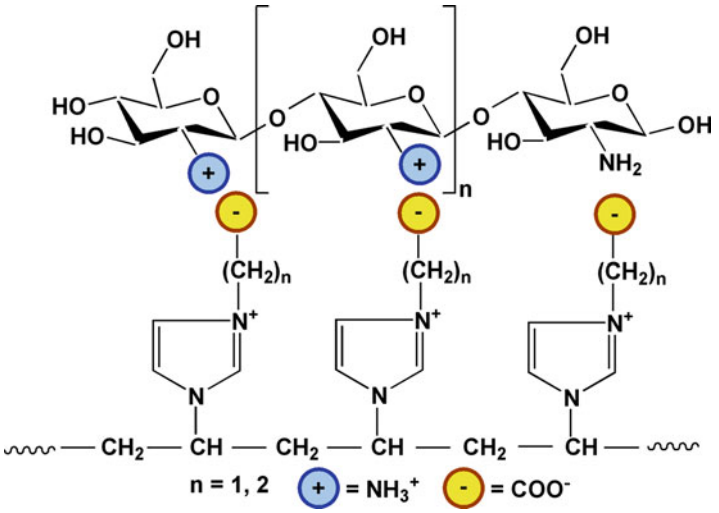


Fig. 4 Graphical representation of the polyelectrolyte complexes between chitosan and poly (carboxybetaines)

Table 1 Preparation conditions of PEC microparticles by the first variant

Sample code	C_{CH} (g/L)	CH solvent	PNVIBL-1 (g)	PNVIBL-2 (g)	T (°C)	t_C (h)
C_1	15	0.1 N CH_3COOH	0.3	–	20	24
C_2	15	0.1 N HCl	0.3	–	20	24
C_3	15	0.1 N CH_3COOH	–	0.3	20	24
C_4	15	0.1 N HCl	–	0.3	20	24

t_C = reaction time

interactions, without excluding the possibility that other types of interactions appear between the two polymers. The hydrogel complex microparticles show good sphericity and the average diameters ranging from 700 to 900 μm. The swelling studies for C microparticles were conducted by means of light microscopy at pH = 5.5 and pH = 7.4.

Usually, the C microparticles show a lower swelling degree in pH = 5.5 than in pH = 7.4 probably due to stronger interactions between chitosan and polybetaines. Also, we noticed when using the second variant of the complex coacervation method for the CH-PNVIBL-2 complex microparticles, the swelling degree in both pHs is influenced by: the solvent used to solubilize the chitosan, temperature and duration of the synthesis reaction of the microparticles, and the ratio of the reaction partners. When the molar ratio between CH and PNVIBL-2 is 1:2, the microparticles present a higher swelling degree. In this case, the swelling can be a consequence of an increase of the hydrophilicity of the C microparticles, a phenomenon also found in case of gellan: PNVIL [39] and chitosan:poly(acrylic acid) complexes [40].

Table 2 Preparation conditions of PEC microparticles by the second variant

Sample code	$C_{PNVIBL-1}$ (g/L)	$C_{PNVIBL-2}$ (g/L)	Molar ratio CH:PCB	CH solvent	T (°C)	t_C (h)
C_5	1.5	–	1:1	0.1 N CH_3COOH	20	24
C_6	1.5	–	1:1	0.1 N HCl	20	24
C_7	–	1.5	1:1	0.1 N CH_3COOH	20	24
C_8	–	1.5	1:1	0.1 N HCl	20	24
C_9	1.5	–	1:1	0.1 N CH_3COOH	20	3
C_{10}	1.5	–	1:1	0.1 N HCl	20	3
C_{11}	–	1.5	1:1	0.1 N CH_3COOH	20	3
C_{12}	–	1.5	1:1	0.1 N HCl	20	3
C_{13}	1.5	–	1:2	0.1 N CH_3COOH	20	24
C_{14}	1.5	–	1:2	0.1 N HCl	20	24
C_{15}	–	1.5	1:2	0.1 N CH_3COOH	20	24
C_{16}	–	1.5	1:2	0.1 N HCl	20	24
C_{17}	1.5	–	1:1	0.1 N CH_3COOH	50	24
C_{18}	1.5	–	1:1	0.1 N HCl	50	24
C_{19}	–	1.5	1:1	0.1 N CH_3COOH	50	24
C_{20}	–	1.5	1:1	0.1 N HCl	50	24

$C_{CH} = 15$ g/L – concentration of chitosan

The increase of the reaction temperature leads to the preparation of C microparticles with high swelling degree. A similar phenomenon was observed in case of chitosan microparticles. When PNVIBL-1 is used, both types of microparticle show approximately the same swelling degree, so the solvent for chitosan does not have any influence on this process. In contrast, it was observed a lower swelling degree at pH = 5.5 for C_5 and C_6 microparticles compared with C_7 and C_8 microparticles. The explanation of this phenomenon may reside in the fact that PNVIBL-2 is more hydrophilic polymer than PNVIBL-1. It is known from literature that the hydrophilicity of polybetaine increases with the increase of the number of methylene groups situated in the zwitterionic unit. At pH = 7.4, the swelling degrees of the C_5 and C_6 microparticles are higher than those of the C_7 and C_8 microparticles. This situation is probably a result of different behavior of the complexes in the phosphate buffer solution, being influenced by the type of poly(carboxybetaine) used in the preparation of the hydrogel complex microparticles.

In order to obtain the new polymer-drug systems, two types of macromolecular supports have been used:

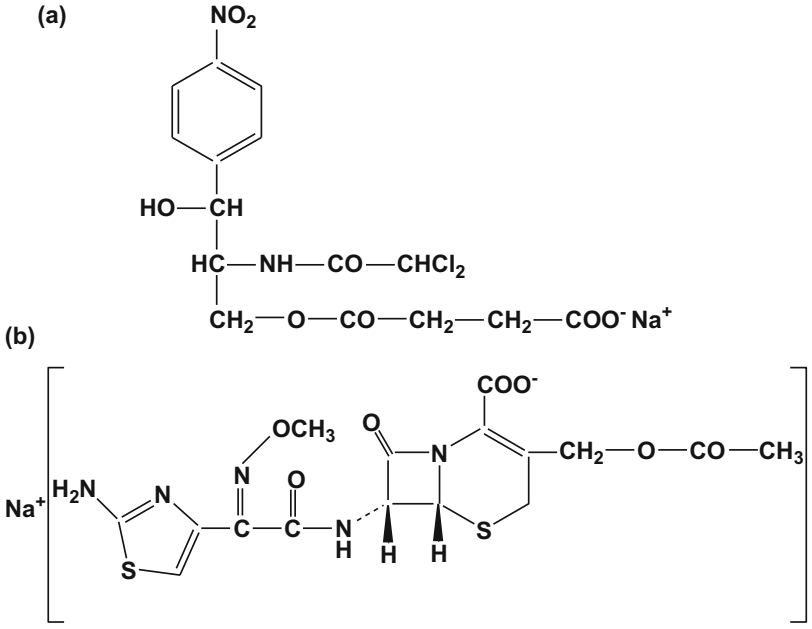
1. Chitosan microparticles obtained by means of simple coacervation technique
2. Chitosan-poly(carboxybetaine) microparticles obtained by means of complex coacervation method

As biologically active principles, two drugs with broad spectrum of activity as antibiotics were selected and the chemical structures of them are presented in Scheme 4.

For CPh and CF adsorption, the physical adsorption method was chosen by immersing the microparticles in drug solutions of certain concentration for different contact times. The quantity of drug retained by the microparticles was calculated as the difference between the quantity of drug present in the solution before and after the retention, being determined spectrophotometrically at 276 nm for CPh and at 236 nm for CF, using the calibration curves for each solution.

Regardless of the nature of the macromolecular supports used, it was found that:

– The adsorption of the two antibiotics was achieved by means of their diffusion from their aqueous solutions into the polymer matrix, the curve allure being similar to those of an adsorption process of a dissolved compound by a solid support, namely retained drug amount increases rapidly in the initial phase of the process, then it reaches a plateau value which means the process equilibrium.



Scheme 4 Chemical structures of antibiotics: (**a**) chloramphenicol succinate sodium salts (CPh) and (**b**) cefuroxime sodium salts (CF)

- The kinetic of drug adsorption processes indicated that CPh and CF penetrate the microparticles since the first moments of immersion in the solution of the two biologically active principles, the process being more intense during the first 60 min. Within 60–120 min, the drug adsorption is slower, tending to stabilize at longer periods of time.
- The retention capacity (Q_{Req}) of the drugs was influenced by the preparation conditions of the microparticles, the nature of the solvent for chitosan dissolution, nonsolvent concentration, and temperature.
- All the samples exhibit a better retention of CF compared to that of CPh, therefore the retention of the amphoteric drug is more favorable then of anionic one. It should be mentioned that the two antibiotics have similar molar weight.
- As expected, the values of the retention capacity at equilibrium increase at the same time with the increasing of the initial concentration of the drug solutions (Fig. 5).
- The studies of drug adsorption showed that the complexes formation between the two polymers led to the retention of a higher quantity of antibiotic compared to the supports based on chitosan [41, 42]. The increased values of Q_{Req} are favored by the values of the swelling degree specific to the complex microparticles, higher than those specific to the chitosan microparticles.

The CF release, the drug which was retained in a higher quantity, from the complex microparticles, depends on their method of preparation. The release rates

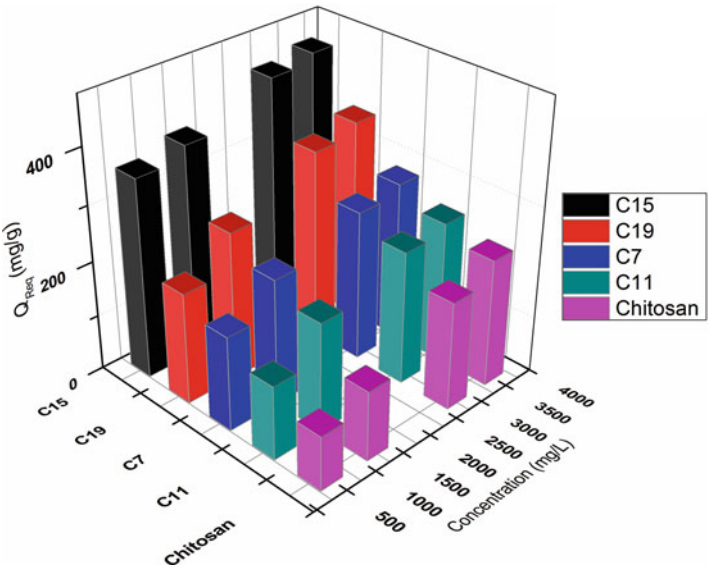


Fig. 5 The retention capacity of CH-PNVIBL-2 polyelectrolyte complexes at equilibrium in function of the initial concentration of CF solution. The solvent for chitosan was 0.1 CH_3COOH

are higher in the first 30 min due to the drug situated in the superficial layers after which they decrease over longer periods of time.

Also, the initial release rate for the complex microparticles is lower than that of the chitosan microparticles, which translates into the release of a smaller quantity of drug in the first minutes of the process. Thus, the "burst effect" phenomenon is diminished, as it was noticed in the case of other systems based on polyelectrolyte complexes.

3.1.2 Chitosan–Poly(acrylic acid) and Poly(methacrylic acid) Polyelectrolyte Complexes

Poly(acrylic acid) and poly(methacrylic acid) are synthetic polyelectrolytes with which chitosan can form PEC, by means of ionic interactions between the amino group of the natural polymer and the carboxylic one situated on the synthetic polymer chains.

The optimum pH range for the preparation of PEC based on chitosan and poly (acrylic acid) is between 2 and 6, because at pH values lower than 2, the poly(acrylic acid) has a low charge density, while at pH values higher than 6, the chitosan becomes insoluble.

PEC based on poly(acrylic acid) and chitosan were prepared in order to be used as:

- Systems for localized delivery of amoxicillin, metronidazole and clarithromycin for eradication of *Heliobacter pylori* [43–45].
- Systems with oral administration of acyclovir [46].
- Films characterized by good flexibility, strength, and bioadhesiveness, which are suitable formulations for inclusion of drugs, which are administered transdermally for the treatment of skin disorders [47].
- Mucoadhesive oral drug delivery system based on interpolymer complex microparticles for enrofloxacin controlled release [48, 49].
- Mucoadhesive films for transmucosal delivery of triamcinolone acetonide. These films were prepared by template polymerization of acrylic acid in the presence of chitosan [50].

Various compositions of polyelectrolyte complexes based on chitosan and Carbopol 974 PNF were prepared by Torre et al. [12, 51] in order to study the polymer/polymer and polymer/amoxicillin trihydrate or amoxicillin sodium interactions. The PEC is formed by the electrostatic interactions between the cationic amino groups of chitosan and the anionic carboxylate groups of poly(acrylic acid).

The release of drugs from polyelectrolyte complex hydrogel was influenced by the nature of drug as follows: the release of nonionized amoxicillin was fast being controlled by the swelling/eroding ratio, while the release of amoxicillin sodium was slower due to the stronger interactions established between drug and the polymer network. In case of amoxicillin trihydrate, the drug is entrapped into the mesh space of the hydrogel. It was concluded that the polyelectrolyte complex hydrogel were the

suitable systems that could be delivered at *Heliobacter pylori* infection sites being useful in the treatment of peptic ulcer.

Varshosaz et al. [52] obtained polyelectrolyte complex hydrogels by means of the reaction between chitosan and Eudragit L 100 and Carbopol 934. Carbopol 934 is poly(acrylic acid) cross-linked with allyl sucrose or allylethers of pentaerythritol, this product being used in lotions and creams.

The Eudragit polymers are synthetic compounds consisting of various ratios of methacrylic acid, dimethylaminoethylacrylate and methacrylic acid esters [53]. Generally, the Eudragit polymers are divided into two categories:

- Polycations such as Eudragit E, RL, RS, and NE that contain the dimethylamino or quaternary amino groups
- Polyanions such as Eudragit L and S that contain the carboxylate groups [54]

Eudragit L100 is an anionic copolymer based on methacrylic acid and methyl methacrylate where the ratio between carboxylic groups and ester ones is 1:1. Usually, Eudragit L100 improves bioavailability, ensures a sustained release of drug being used as an enteric coat for tablets. The authors showed that the hydrogels based on chitosan and Carbopol 934 and chitosan: Eudragit L100 are ideal drug carriers for the preparation of tablets with sustained release of bupropion hydrochloride, an antidepressant drug from the amino-ketones group prescribed in the treatment of nicotine addiction as support for smoking cessation.

The ionic interaction between chitosan and Eudragit has been highlighted for the first time in case of colon targeted drug delivery systems. The simplest method for slowing the release rate and extend the release period is to apply a thin layer of enteric coating on the surface of colon targeted drug delivery systems. These systems were prepared in two steps: (i) sodium diclofenac was entrapped within chitosan microcores using spray-drying method; (ii) the CS microcores were incorporated into Eudragit L-100 and Eudragit S-100 using an oil-in-oil solvent evaporation technique. The release process was affected by various factors such as size and swelling behavior of chitosan microcores, the ratio between microcores and acrylic polymers, type and pH solubility of Eudragit [55].

3.1.3 Chitosan–Other Synthetic Polyanions Polyelectrolyte Complexes

Poly(alkylenoxide-co-maleic acid) copolymers (PAOMA) are the synthetic anionic polymers possessing the amphiphilic properties being also characterized through an excellent biocompatibility. Films based on PAOMA with different chemical structure and characteristics (hydrophobic and hydrophilic) and chitosan were prepared as pH- and temperature-sensitive drug delivery systems. In this case, salicylic acid and phenol were used as model drugs. It was found that the drug release from PEC films is influenced by the type of PAOMA (hydrophobic or hydrophilic), the pH, and the temperature [56].

In case of polyelectrolyte complexes between polyphosphoric acid and chitosan, the three dimensional network is formed by the reaction between $-[P_2O_5^{4-}]-$ group

from polyphosphoric acid and $-NH_3^+$ group belonging to chitosan. Chitosan-polyphosphoric acid gel beads are an alternative to obtain the nontoxic polymer carriers for the sustained release of 6-mercaptopurine in simulated intestinal and gastric fluid solutions [57]. 6-mercaptopurine is a drug used in the treatment of cancer, especially acute lymphocytic leukemia and chronic myeloid leukemia and autoimmune disease as inflammatory bowel diseases (Crohn's disease and ulcerative colitis) [58, 59]. The released studies indicate that the chitosan-polyphosphoric acid gel beads are the suitable polymeric carriers for the controlled/sustained release of anticancer drug compared to the chitosan-tripolyphosphate gel beads.

3.2 Polyelectrolyte Complex Hydrogels Based on Chitosan and Natural Polyanions

Many different polyanions from natural origin have been used to form polyelectrolyte complexes with chitosan to improve the physicochemical properties of the components generally in order to design drug delivery systems with specific applications. Even chitosan forms polyelectrolyte complexes with many natural compounds like collagen, gelatin, silk fibroin, DNA, we decided to treat in this chapter the most of the investigated chitosan PEC's which are formed with other natural polysaccharides, including phytopolysaccharides, zoopolysaccharides, and microorganism polysaccharides [60].

In Fig. 6, the structure of chitosan and of the most investigated polysaccharides for PECs formation are presented.

3.2.1 Chitosan–Alginate Polyelectrolyte Complexes

Alginate is a natural, linear, unbranched, biodegradable polysaccharide extracted from brown seaweeds and marine algae (such as *Laminaria hyperborea*, *Ascophyllumn odosum,* and *Macrocystis pyrifera)* consisting of 1,4-linked β-D-mannuronic acid and α-L-guluronic acid monomers in different proportions. Being biodegradable and biocompatible (its hydrogel has a similar structure to extracellular living tissue) [61], it is intensively used in medical, pharmaceutical, and food applications.

The chitosan–alginate polyelectrolyte complex is formed by electrostatic interaction between the negatively charged carboxylic acid groups of mannuronic and guluronic acid units in alginate with the positively charged amino groups of chitosan and is one of the most studied PEC of chitosan due to the fact that this remains biodegradable and biocompatible but mechanically stronger at lower pH values where chitosan dissolves [62].

Micro- and nanoparticles, composites, membranes, fibers most of them with hydrogel characteristics have been prepared and characterized in order to study their applicative potential. Because of the space limitations and of the high number of contributions on the chitosan-alginate PECs, the authors of this chapter decided to present only few examples which are in their opinion the most representative and recent.

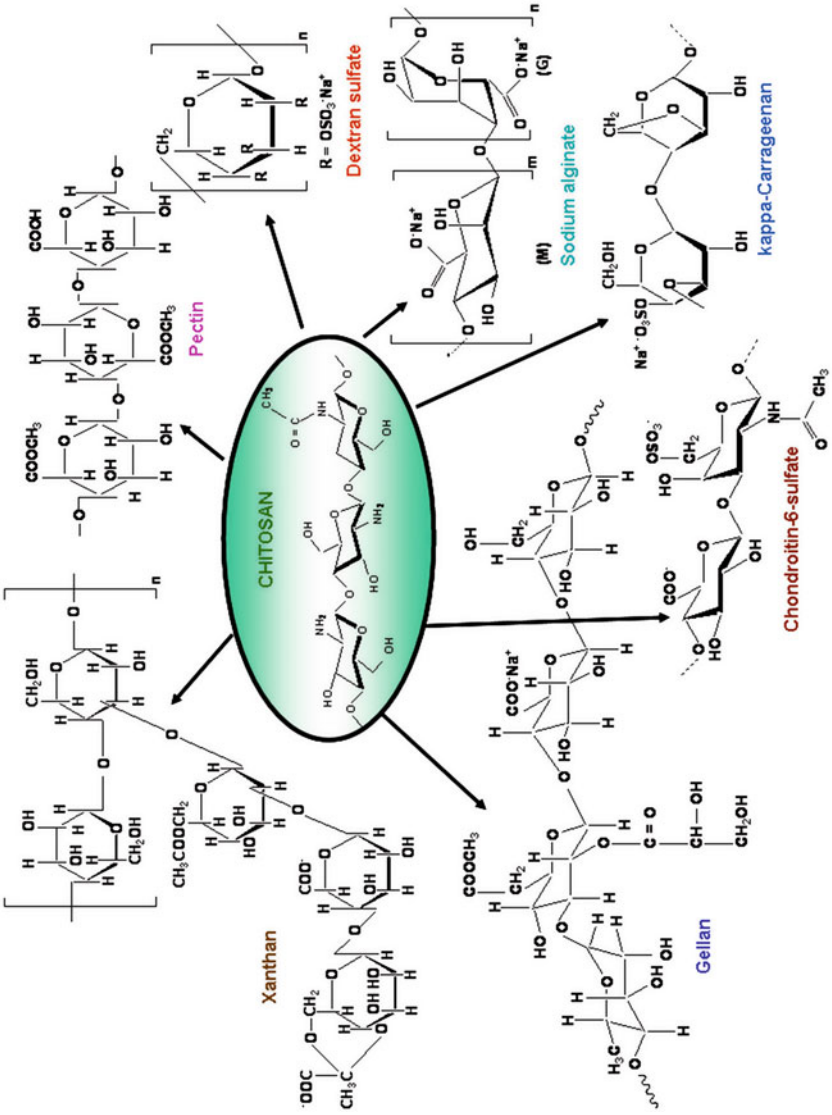


Fig. 6 The structures of chitosan and polysaccharide polyanions used for PECs formation

Very recently, the research group of Kim obtained highly porous composites with antimicrobial properties from chitosan, alginate, and silver nanoparticles (AgNPs). In this case, chitosan- and alginate-based PEC was used as biocompatible and degradable matrix for AgNPs with antimicrobial properties [63].

Quercetin has been successfully encapsulated by Tzankova et al. [64] in chitosan/alginate nanoparticles prepared by electrostatic gelation method which means that the nanoparticles present a hydrogel character. Investigating the nanoparticles antioxidant and hepatoprotective effects, the authors proved the lack of cytotoxicity in human hepatoma HepG2 cells and a good safety profile in vitro.

A very interesting biomedical application of chitosan–alginate PEC is represented by nanoflowers obtained from 5-fluorouracil – cyclodextrin inclusion complex as core which was covered by alginate – chitosan PEC as petals. The encapsulation efficiency of the inclusion complex in PEC has been very high (80%), the final nanoflowers it seems that are nontoxic and pH dependent, the latter property being in direct relation with the swelling degree of the *petals* [65].

Nanofibers impregnated with silver nanoparticles as hydrophilic biocomposites with antibacterial properties has been obtained by Mokhena and Luyt using chitosan–alginate PEC which it seems that influence the release of silver nanoparticles from the system [66].

3.2.2 Chitosan–Carrageenan Polyelectrolyte Complexes

Carrageenan is a polysaccharide extracted from red seaweed, and it is composed by galactose and anhydrogalactose units, linked by glycosidic bonds. Carrageenan displays a strong ionic nature because of the presence in its structure of half ester sulfate moieties. There are three main types of carrageenans: β, κ, and λ which mainly differ structurally in the degree of substitution of the sulfate group, but only from β and κ present the gel forming ability [67].

The chitosan–κ-carrageenan results through binding the negatively charged sulfate groups of κ-carrageenan to the positively charged amino groups of chitosan in acid conditions.

Taking into account that chitosan is nontoxic and presents excellent biocompatibility, antiseptic, mucoadhesiveness, and that carrageenans is demonstrated to have anticoagulant, anticancer, antihyperlipidemic, and immunomodulatory activities [68], chitosan–carrageenans PECs are considered that might give combined properties.

In order to avoid the lack of stability in gastric pH of the PECs, Li et al. used salt (NaCl) induced impeding of polyplex formation method and they obtained a homogeneous bovine serum albumin loaded chitosan–carrageenan PEC hydrogel particles stable in acidic pH [69].

Ovalbumin-loaded chitosan–carrageenan nanoparticles with sizes under 650 nm and positive zeta potentials were obtained by ionic complexation between the two polysaccharides. The hydrogel nanoparticles are able to release in a sustained manner the protein for 3 weeks and they present low toxicity in contact with fibroblast-like cells [70].

Chitosan–carrageenans nanoparticles with reduced size, strong positive surface charge, and higher stability have been prepared by Rodrigues et al. using sodium tripolyphosphate as ionic crosslinker showing their potential to be used in mucosal drug delivery [71].

Isoniazid (tuberculostatic drug) loading hollow nanocapsules of κ-carrageenan and chitosan have been prepared by encapsulating in the first step the neem seed oil which was then removed and replaced with isoniazid. For increasing the stability of nanoparticles, a natural crosslinker, genipin, has been used. The release rate of isoniazid was dependent on the pH of the medium [72].

Solid formulations based on chitosan, κ-carrageenan, and semisynthetic hydroxyl-propyl-methylcellulose have been developed by Sánchez et al. for the controlled release of acyclovir (which may prevent the sexual transmission of the herpes simplex virus) [73]. It was demonstrated that the formulations are biocompatible in vitro, bioadhesive to vaginal mucosa and that acyclovir could be released for a period of 8–9 days.

3.2.3 Chitosan–Chondroitin Sulfate Polyelectrolyte Complexes

Chondroitin sulfate (CS), a polysaccharide which can be extracted from bones, cartilages and connective tissues, skin, corneas, and umbilical cords, consists in n-acetylgalactosamine and glucuronic acid residues alternately linked to each other by the β 1,4 and β 1,3 bonds, respectively. Chondroitin sulfate is an acidic mucopolysaccharide able to form ionic complexes with positively charged chitosan [74]. Due to the presence of SO_4^{2-} and COO^- in the molecule, chondroitin sulfate has a high negative polarity allowing to be used as polyanion in PEC formation.

Micro- and nanoparticles, hydrogels, layer-by-layer membranes using chitosan–chondroitin sulfate PECs have been intensively studied proving every time their biomedical applicative potential. Representative examples will be further briefly presented.

In comparison with other polysaccharides, chondroitin sulfate is often used as bioactive principle being a good cartilage repair agent. Bianchera et al. [75] prepared hydrogels from chitosan and chondroitin sulfate and studied the influence of pH used for loading on the release rate of the latter. The pH influence the porosity of the scaffolds and, consequently, the amount of CS released from the scaffolds loaded at pH 4.5 is significantly lower than the amount released from scaffolds loaded at pH 6 and 8. In conclusion, it is possible to modulate the amount and the release rate of chondroitin sulfate and to obtain a certain release profile.

Complex microcapsules based on chitosan and chondroitin sulfate were prepared by emulsion-crosslinking method using heparin (indicated in prevention and treatment of thrombosis) as the core material [76]. Microcapsules with size between 20 and 80 μm present a relatively high porosity facilitating the release of heparin.

Daley et al. [77] embedded mesenchymal stem cells (MSC) in chitosan–chondroitin PEC particles for the treatment of joint injuries and osteoarthritis. These researchers designed a complex 3D modular microtissue which maintained the high cell viability over 3 weeks in culture.

Doxorubicin-loaded nanoparticles with antitumoral effect have been prepared by ionic gelation method from the same PEC by Hu et al. [78]. In vitro, the nanoparticles were taken up by the hepatoma cell in a higher proportion than doxorubicin solution and in vivo were more effective to achieve less body weight loss and antitumor growth suppression in the xenograft mouse model.

The research group of Abdullah has investigated for the first time the potential of chitosan–chondroitin sulfate nanoparticles in ophthalmological delivery of bromfenac [79]. The nanoparticles with a medium size of 250 nm prepared by ionic gelation method showed high transcorneal permeation and retention of bromfenac and also can be considered nonirritant for the eye.

3.2.4 Chitosan–Dextran Polyelectrolyte Complexes

Dextran is a branched polysaccharide with 1,6 and 1,4 glycosidic linkage and contains approximately 16–19% sulfur, which is equivalent to approximately 1.6–2.4 sulfate groups per glucosyl unit and forms PEC with chitosan in a similar manner through sulfate and ammonium groups. The applicative potential of chitosan–dextran sulfate PEC is huge due to their properties, and because of the space limitations in the next paragraphs, only few representative examples are briefly presented.

Curcumin-loaded nanoparticles with 200–220 nm have been prepared and investigated by Anitha et al. [80]. Curcumin, a natural antitumoral agent, has been released for more than 1 week and it seems that curcumin-loaded nanoparticles are killing preferentially the cancer cells proving the immense potential of these formulations in cancer therapy.

Topical ocular drug delivery can be improved by using chitosan–dextran sulfate nanoparticles; for example, it was investigated the possibility of lutein (reduce the risk of vision loss in cataracts and/or age-related macular degeneration) encapsulation within such nanoparticles [81]. The nanoparticles with sizes under 500 nm are suitable for topical eye administration since they are completely nontoxic; they present high lutein entrapment efficiency and they are mucoadhesive due to the presence of chitosan.

Antibiotic like ciprofloxacin, ceftriaxone, or gentamicin could be encapsulated in chitosan–dextran nanocapsules which will efficiently to kill intraphagosomal bacteria (for example, Salmonella) inside cells in treatment of infective diseases [82]. Using these nanocapsules prepared by layer-by-layer technique, a significantly lower dose than of the free antibiotic is necessary for an efficient targeting.

Very recently, hydrogels and beads based on chitosan and dextran sulfate crosslinked with a natural crosslinker, genipin, have been investigated with promising results for their potential to encapsulate probiotic cells by Falco et al. [83].

3.2.5 Chitosan–Gellan Polyelectrolyte Complexes

Gellan gum is an anionic heteropolysaccharide produced by fermentation of a pure culture of *Sphingomonas elodea* composed of repetitive units of tetrasaccharides consisting of two β 1,3 D-glucoses, one β-1,4-D-glucuronic acid, and one α-1,4 L-ramnose ring. Commercially, the gellan gum is obtained with low and high acyl

content [84]. Gellan gum with low acyl content presents a strong affinity for divalent cations and, consequently, it is able to form gels at relative low concentrations [85]. At high temperatures, gellan presents a coiled conformation and when the temperature decreases aggregates and forms double helices. As almost any other natural polysaccharide, gellan gum is a nontoxic, biocompatible, and biodegradable.

The applicability of chitosan–gellan gum polyelectrolyte complex has been intensively explored especially as drug delivery systems. Calcium crosslinked beads prepared by ionotropic gelation and polyelectrolyte complexation have been investigated for their ability to encapsulate and release proteins such as bovine serum albumin by Yang et al. [86]. In order to meet the dosage needs, the loading and release ability of the beads can be adjusted by changing the crosslinking reaction parameters like concentration of chitosan, calcium, and gellan gum, the appropriate formulations might be successfully use for protein oral delivery.

Very recently, stable chitosan–gellan nanogels loaded with curcumin for cancer therapy were obtained by Mahajan et al. [87] by gelation technique. Nanogels are nontoxic and hemocompatible, present good curcumin entrapment efficiency and sustained release.

Ketoconazole-loaded chitosan–gellan nanoparticles were prepared and tested for their antifungal activity against *Aspergillus niger* [88]. It was observed that the nanoparticles size and zeta potential can be adjusted by varying the gellan amount and concentration in the initial composition, and consequently, the density of the network will change. The PEC nanoparticles proved antifungal activity for more than 7 days.

Rifampicin, a poorly soluble antibiotic used in the treatment of tuberculosis, has been encapsulated by Patil et al. [89] in gellan gum hydrogel-based microbeads prepared by ionotropic gelation method and coated with chitosan through polyelectrolyte complexation. In order to improve the rifampicin solubility, cyclodextrin was also used as solubility enhancer. Some of the formulations were developed with cyclodextrin as a solubility enhancer for poorly soluble rifampicin in the polymer matrix. Using this quite simple and nontoxic system, it was possible to maintain constant the drug level for 24 h which might have a positive impact on the administration frequency.

3.2.6 Chitosan–Xanthan Polyelectrolyte Complexes

Xanthan gum is a microbial polysaccharide that can be produced from simple sugars using a fermentation process and its name derives from the strain of bacteria used in this: *Xanthomonas campestris.* The molecule of xanthan gum is composed from a cellulosic backbone with two mannose and one glucuronic acid side chains on every second glucose residue. Due to its molecular weight which can reach up to 6 million Daltons [90], xanthan is a common food additive, especially as thickening agent.

Xanthan is considered an anionic polyelectrolyte due to the presence in its side chains of glucuronic acid and pyruvate, and for this reason, it is possible to form PEC with polycations like chitosan. These complexes present promising candidates for controlled drug delivery mainly due to their nontoxic nature and pH sensitive swelling/release properties [91].

Even xanthan has properties which make him suitable for a wide range of applications, the high molecular weight and high viscosity of solutions at very low concentration limit somehow the interest of researchers. The literature does not report too many studies considering the abundance of other natural polyanions.

An interesting aspect was remarked by Shchipunov et al. [92] regarding the morphology of the chitosan–xanthan PEC hydrogels. In comparison with all other polysaccharides, this complex self organizes in fibrils when pH changes and this property is related to the xanthan ability to self-assembly into a double helix making the system highly rigid.

Xanthan–chitosan polyionic complex as capsules loaded with theophylline, a bronchodilator drug used in chronic obstructive pulmonary disease, has been prepared and analyzed by Popa et al. [93]. The morphology of capsules revealed the fibrillar structure of the complex and the release profile of the drug proved the stability of the complex in both acidic and basic pH.

Liposomes coated with chitosan–xanthan gum (chitosomes) were prepared and analyzed as potential carriers for pulmonary delivery of rifampicin used in antituberculosis therapy [94]. Rifampicin-loaded liposomes and chitosomes were compared for their suitability to be delivered to the lungs by nebulization therapy, the results showed a higher encapsulation efficiency of rifampicin for chitosomes and an improved resistance of liposomes to aerosolization.

3.2.7 Chitosan–Hyaluronic Acid Polyelectrolyte Complex

Hyaluronic acid (HA) is an anionic polysaccharide present in all living organisms, which is, at the same time, an universal component of the space among the cells of the body tissue. In 1980, Portes found in the vitreous body a substance similar to mucin but with a different structure from others mucoid components in cornea and cartilages, which he called hyalomucin. It was only in 1934 when Meyer and Palmer isolated a substance they named hyaluronic acid starting from the vitreous humour of the ox eye and which they described as an acidic polysaccharide with high molecular weight. The chemical structure was elucidated latter in 1962 when it was proved that hyaluronic acid is a linear polymer and that the disaccharide moieties which repeats itself is made of N-acetyl-D-glucosamine and β-D-glucuronic acid linked through glycosidic (1,3) and (1,4) alternating linkages. Hyaluronic acid plays an important role in: macrophages and granulocytes activation, cell protection, migration and cell differentiation control in the process of growing. Although for a long period of time, hyaluronic acid was extracted from rooster comb, today it is obtained, with very good results, through the fermentation method, which also has the advantage of getting an impurity-free polymer. Because of its outstanding rheological properties and biocompatibility, the hyaluronic acid is widely used in the medical field, namely: ophthalmology, arthritis treatment, wound treatment, tissue engineering, and even coating or component of implants.

It is very well-known that the polyelectrolyte complexes are formed between pK_a of the polyanion and pK_b of the polycation [95]. In the case of chitosan ($pK_b = 6.5$) and hyaluronic acid ($pK_a = 2.9$), it was shown that the process of the polyelectrolyte complex formation take place in two stages: (a) deprotonation of the carboxyl groups

of HA; (b) reaction between ammonium groups of chitosan and carboxylate groups of hyaluronic acid via electrostatic interactions [96, 97]. Important contributions regarding the stability of the PEC between chitosan and hyaluronic acid were made by Rusu Balaita et al. [98].

In biomedical applications, PECs based on chitosan and hyaluronic acid have shown a great interest due to the properties of both polymers.

PEC based on chitosan and sodium hyaluronan were obtained as microparticles by two methods. The first method is based on complex coacervation by adding dropwise a solution of chitosan of different concentrations to the hyaluronan solution. By the second method firstly, the chitosan particles were obtained by the simple coacervation technique, followed by the complex preparation through the suspension of the particles in a solution of hyaluronan. It was found that the particle size and morphology depend on a number of factors: concentration of polyion solutions, pH value, and complexation time. Microparticles with a hydrogel character have shown stability in water and acid medium, high water swelling capacity, and high inclusion capacity of some active ingredients such as cefotaxime sodium salt and dextran. Also, the microparticles based on polyelectrolyte complexes have shown a sustained release of drugs [99, 100].

A new oral delivery system based on chitosan/hyaluronic acid-paclitaxel nanoparticles with pH-sensitive and tumor targeting characteristics were obtained in two steps:

1. Preparation of hyaluronic acid-paclitaxel conjugate nanoparticles via esterification reaction. Paclitaxel, well-known as Taxol, is a mitotic inhibitor used to treat various types of cancer such as: ovarian, breast, lung, head, and neck cancers and sarcomas [101].
2. Preparation of chitosan/hyaluronic acid-paclitaxel nanoparticles by coating chitosan onto hyaluronic acid-paclitaxel via electrostatic interactions at different charge ratio ($-NH_3^+/COO^-$).

For the studies undertaken, the following conclusions can be drawn: (a) because HA is biocompatible with $HepG_2$ and NIH-3 T3 cells, the release of paclitaxel from PEC nanoparticles can occur without loss of cytotoxicity; (b) the ex-vivo biodistribution experiments showed that paclitaxel could accumulate very well into tumor sites, after oral administration of PEC nanoparticles, thus the PEC nanoparticles could be used as a potential carriers for the oral delivery of anticancer drug [102].

A similar system based on chitosan-coated hyaluronic acid-docetaxel conjugate nanoparticles was obtained to improve docetaxel availability. Like paclitaxel, docetaxel is part of taxoid class of antineoplastic agents being commercially available under the brand name Taxotere. This medication is used to treat some types of cancer such as breast, ovarian, head, neck, prostate, stomach, renal, colorectal and non-small cell lung cancers, as well as miscellaneous tumors [103]. The biological evaluation confirmed that the chitosan-coated hyaluronic acid-docetaxel nanoparticles present appropriate entrance into MCF-7 and 4 T1 cells and are more effective against $CD44^+$ cells than free docetaxel [104].

Luppi et al. [105] were developed a novel mucoadhesive nasal inserts based on chitosan/hyaluronate polyelectrolyte complexes for vancomycin and insulin delivery. The polyelectrolyte complexes have been obtained by changing of some parameters such as pH and molar ratio between chitosan and hyaluronan. Selection of optimum conditions for the preparation of inserts leads to the improvement of muchoadhesion potential, swelling capacity, and drug release behavior. Also, the microparticles based in chitosan-HA polyelectrolyte complexes prepared by water-in-oil emulsification and solvent evaporation technique have been used as nasal drug delivery systems being characterized by a high encapsulation efficiency and very good mucoadhesive properties [16].

In tissue engineering, the major problem in scaffold manufacturing is the selection of suitable materials that should be biocompatible and biodegradable, must present a highly porous structure, and also a similar architecture as the extracellular matrix [106].

Lindborg et al. [107] were developed a hydrogel formed by CH-HA polyelectrolyte complex fibers namely Cell-Mate3D that presents the ability to maintain the cell viability as well as to allow the differentiation of the human mesenchymal stem/stromal cells into adipogenic, chondrogenic, and osteogenic phenotypes, indicating that this material can be used in applications such as tissue engineering, regenerative medicine, and cancer stem cell biology.

Wetspinning method and electrospinning were employed to obtain chitosan–-hyaluronic acid fibers as scaffold materials that can be applied to the treatment of the cartilage lesions caused by osteoarthritis and rheumatoid arthritis. Based on the studies conducted, it has been demonstrated that the scaffolds based on CH-HA fibers present adequate strength, high cellular adhesivity being an excellent support for chondrogenesis [108, 109].

The PEC based on chitosan and hyaluronic acid was chosen as carrier for immobilization and controlled/sustained release of bone morphogenic protein-2 (BMP-2), a protein that has the capacity to induce bone formation [110].

By this method, it has achieved an improvement of pharmacokinetic parameters (half-life and clearance) as well as of the attachment and proliferation of the pre-osteoblasts cells [111].

Chitosan and hyaluronic acid have been widely used as wound dressing due to their remarkable properties: nontoxicity, antimicrobial and hemostatic activity, stimulation of healing. For this reason, the chitosan/hyaluronic polyelectrolyte complex hydrogel represents an ideal support for the preparation of the bandages that can be applied successfully in the management of burn wounds [112].

4 Conclusion

As shown in this chapter, the polyelectrolyte complexation method is an excellent way to prepare the materials based on the synthetic and natural polyelectrolytes, because the PECs formation is the spontaneous process and take place in aqueous solution and without adding other substances such as catalysts, initiators, and chemical crosslinking

agents, thereby reducing the toxicity of these materials. Materials based on synthetic and natural polyelectrolytes have gained an increased interest throughout the twentieth century, being used in a large number of applications in both the industrial and the medical fields. Polyelectrolyte complexes can be prepared with different shapes and geometries including nano/microparticles, hydrogels, sponges, membranes, films, etc. Among these materials, the chitosan-based polyelectrolyte complex hydrogels with various synthetic [polybetaines, poly(acrylic acid), poly(methacrylic acid)] and natural (alginate, carrageenan, chondroitin sulfate, dextran, gellan, anthan, hyaluronic acid) polyanions have the structures and properties similar to those of biological tissue and are very well tolerated by the organism, making them to be the excellent candidates for biomedical applications: oral drug delivery, ocular drug delivery, nasal drug delivery, wound healing, and tissue engineering.

5 Future Scope

The fabrication of the new polyelectrolyte complex hydrogels which can be tailored with desired properties represents a challenge for the future. Knowing that the most interesting properties of polybetaine are bio- and hemocompatibility, the development of polymeric coating based on polybetaines-chitosan polyelectrolyte complexes can lead to improve the biocompatibility of devices used in various therapies (ocular and tissue engineering) by decreasing adhesion of microorganisms and eukaryotic cells. Also, in situ forming polyelectrolyte complex hydrogels represent the future in intelligent drug delivery systems and in tissue engineering as scaffold for proliferation and differentiation of cells.

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Interpenetrating Polymer Network Hydrogels of Chitosan: Applications in Controlling Drug Release

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Abstract

Chitosan is a natural polysaccharide obtained by alkaline deacetylation of chitin. It is cationic in ionic nature. Because of its biocompatibility and biodegradability, chitosan is employed as a drug carrier material in the development of various kinds of drug delivery. However, the extensive use of chitosan as a drug delivery carrier material is limited by its rapid dissolution in the acidic pH of the stomach, and this causes restrictions in controlling drug release from chitosan-based oral dosage forms. To overcome this limitation, modifications of chitosan to develop hydrogel systems are being investigated by researchers. Among these modified chitosan-based hydrogel systems, interpenetrated polymer network (IPN) hydrogels have enhanced mechanical properties at gastric pH, as well as improved control of drug release over a longer period. This chapter describes the preparations and properties, in terms of drug-releasing performance, of various chitosan-based IPN hydrogels for controlling drug release.

Keywords

Chitosan · Interpenetrating polymer network (IPN) · Hydrogel · Oral dosage forms · Drug release

1 Introduction

Chitin was first discovered in 1811 by Henry Braconnot, during studies conducted on mushrooms. The word "chitin" is derived from a Greek word meaning "tunic." A linear aminopolysaccharide of glucosamine and *N*-acetylglucosamine units, which was named "chitosan" (pronounced "kite-o-san") by Hoppe-Seiler, is obtained by alkaline deacetylation of chitin extracted from the exoskeleton of crustaceans, such as shrimps and crabs, and the cell walls of some fungi [1]. Chitosan was initially used as a hemostatic agent and then as a water purification agent and supplement for weight loss. Chitosan have various advantages for use in applications, as it has a defined chemical structure, which can be chemically and enzymatically modified for physical and biological functionality, and it is biodegradable and biocompatible?. The structure of chitosan is shown in Fig. 1.

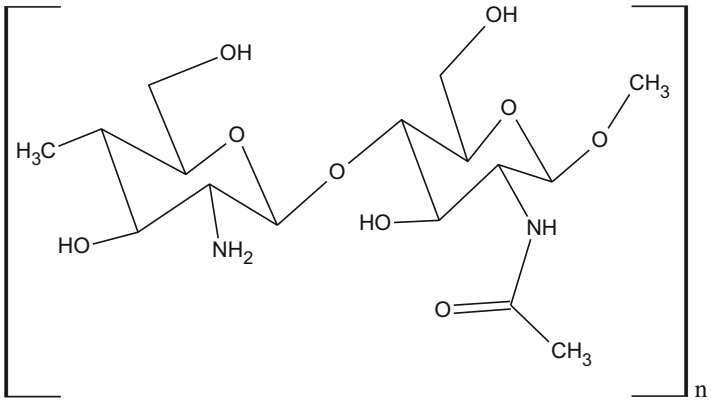


Fig. 1 Structure of chitosan

2 Production of Chitosan

The raw materials for chitosan are abundantly available as the shells of crab, shrimp, and prawn. Through treatment with sodium hydroxide or digestion in the presence of proteolytic enzymes such as papain, proteins are removed from the ground shells. Calcium carbonate and calcium phosphate are extracted out with hydrochloric acid treatment [2]. Melanin and carotenoids are washed out by treatment with 0.02% potassium permanganate at 60 °C. Conversion of chitin to chitosan is achieved by hydrolysis of acetamide groups of chitin. Thermal treatment of chitin with a strong aqueous alkali such as sodium hydroxide or potassium hydroxide (40–50% at 100 °C) to remove some or all of the acetyl groups from the polymer produces partially deacetylated chitin, regarded as chitosan. Also, a deacetylation reaction is carried out in the presence of thiophenol as a scavenger of oxygen or under an N_2 atmosphere to prevent chain degradation, which invariably occurs because of a peeling reaction under strong alkaline conditions [3]. The scheme for the production of chitosan is shown in Fig. 2.

3 Physiochemical Properties of Chitosan

3.1 Crystalline Structure of Chitosan

Chitosan is a heterogeneous polymer consisting of glucosamine (GlcN) and *N*-acetyl glucosamine (GlcNAc) units; its properties depend on the structure and composition. The crystalline structure of different chitin or chitosan samples is prepared by one of two different procedures: (a) partial deacetylation of chitin; or (b) partial reacetylation of fully deacetylated chitin. A less crystalline

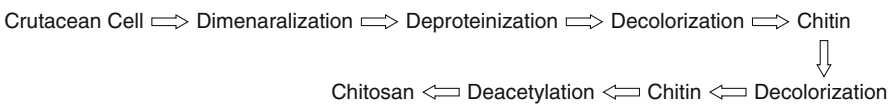


Fig. 2 Production of chitosan

chitosan sample is produced by reacetylation of fully deacetylated chitosan rather than direct solid-state deacetylation of chitin. Production of less crystalline chitosan also depends on secondary treatment such as reprecipitation, drying, and freeze drying [4].

3.2 Degree of *N*-Acetylation of Chitosan

The ratio of GlcNAc to GlcN structural units is the important factor in the structure of chitosan and has a direct effect on the solubility of chitosan. In chitin, the acetylated unit prevalence is $\geq$90%, whereas chitosan is a fully or partially *N*-deacetylated derivative with a degree of acetylation of <30%. Assessment of the degree of deacetylation of chitin determines what deacetylation conditions are suitable to make quicker preparation of chitosan feasible [5]. The quality of chitosan depends on the source of chitin and its process of isolation. The appearance of the polymer, the turbidity of the polymer solution, the degree of deacetylation, and the molecular weight are the main characteristics of chitosan polymer. Chitosan obtained from deacetylation of chitin becomes soluble in aqueous acidic solutions when the average degree of deacetylation is above 0.5, but not at an alkaline or physiological pH. The physical properties of chitosan in an aqueous solution of chitosan depend on the degree of deacetylation and the acetyl group distribution in the polymer chains. Acetyl group distribution in an uneven way will lower the solubility of chitosan. A problem with the solubility of chitosan always hinders its applicability domain [6]. At the molecular level, modification of chitosan increases its solubility and stability, and thus it behaves as a versatile biopolymer. Chitosan hydrogel is one of its most important composites; it is composed of a crosslinked network of polymer chains with a high content of hydrophilic groups. Although it is superabsorbent of water, the chemical or physical bonds in between the polymeric chains make them water insoluble. Hydrogels are polymeric crosslinked network structures. The hydrogel structure is obtained with the presence of hydrophilic groups in a polymer network upon hydration in an aqueous environment. Hydrogels are broadly classified into two categories. Permanent/chemical gels are covalently crosslinked networks (replacing hydrogen bonds with stronger and stable covalent bonds), which establish an equilibrium swelling state based on the polymer–water interaction parameter and the crosslink density. In reversible/physical gels the networks are held together by molecular forces such as ionic, hydrogen bonding, or hydrophobic interactions [7]. In physically crosslinked gels, dissolution is prevented by physical interactions between different polymer chains. All of

these interactions are reversible and can be disrupted by changes in physical conditions or application of stress. Hydrogels are prepared by chemical or physical crosslinking processes. Methods for chemical crosslinking of hydrogels include (1) radical polymerization, (2) photopolymerization, (3) enzymatic reactions, and (4) covalent crosslinking via linkers. Physical crosslinking forms a nonpermanent network with physical interactions by hydrogen or electrostatic bonds, physical entanglements, and crystal formation. Physically crosslinked hydrogels are formed via ion interactions, graft copolymers, crystallization, and stereo complex formation [8].

4 Modifications of Chitosan

4.1 Hydrophobic Chitosan

Attachment of a hydrophobic moiety to the original structure of chitosan using covalent linkage is the process used to increase hydrophobicity. This hydrophobic interaction may enhance the stability of substituted chitosan by reducing the hydration of the matrix and also creates resistance to degradation by proteolytic enzymes. pH-sensitive chitosan can be produced by introduction of carboxylic acid groups into its structure. In an acidic environment the carboxylic groups exist in a nonionized form and therefore the chitosan polymer is poorly soluble in water, whereas in alkaline conditions the chitosan polymer is ionized and is considerably more hydrophilic. The hydrophobic excipient is expected to increase the mucoadhesivity through hydrophobic interactions. One of the approaches used to induce hydrophobic characteristics of chitosan is introduction of hydrophobic groups through addition of long-chain acyl chlorides and anhydrides into the chitosan structure.

4.2 Hydroxyalkyl Chitosans

Epoxidation of chitosan produces various derivatives of chitosan. *N*-hydroxyalkyl or *O*-hydroxyalkyl chitosans are widely applied in gene delivery [9].

4.3 Quaternized Chitosan

Quaternization or methylation of chitosan gives it enhanced solubility in neutral and alkaline environments of the intestine, which makes it more efficient than the parent chitosan for absorption across intestinal epithelial cells. Trimethylated chitosan (TMC) is prepared by reaction of chitosan with trimethyl iodide. TMC nanoconjugates with 35% quaternization contribute good penetration enhancement and mucoadhesive properties. *N*-hydroxypropyl trimethylammonium chitosan chloride (HTCC), which is obtained by reaction

of chitosan with glycidyl trimethylammonium chloride, is preferred for oral insulin delivery.

4.4 Polyethylene Glycol–Grafted Chitosan Derivatives

The reaction between chitosan and polyethylene glycol (PEG), followed by reductive alkylation of an amino group of chitosan, helps to form grafted chitosan nanoconjugates. PEG with hydrophilic chitosan nanoparticles is used as an anionic drug carrier.

4.5 Thiolated Chitosan

To improve the permeation effect, thiolation of polymers confers the attribute of strong mucoadhesivity. Thiolation is done by derivatization of the primary amino groups of chitosan with thioglycolic acid, 2-iminothiolane, cysteine, and thiobutylamidine. Thiolated chitosan is also known for its in situ gelling features due to pH-dependent formation of intermolecular and intramolecular disulfide bonds. Chitosan–cysteine conjugates, chitosan-4-thio-butyl-amidine conjugates, and chitosan–thioglycolic acid conjugates are the three important types of chitosan conjugate. Trimethyl chitosan–cysteine conjugate (TMC-Cys) is used in vivo for oral delivery of docetaxel. Also, mono-*N*-carboxymethyl chitosan, *N*-sulfo-chitosan, and trimethylated chitosan are effective because of their mucoadhesive properties [10].

4.6 Chitosan and Sugar

To increase the water solubility of chitosan in a wide range of pH environments, sugar derivatives are synthesized, which are formed by amide linkage between chitosan and hydrophilic sugar moieties. Chitosan with monosaccharide and disaccharide composites occur via a chitosan *N*-alkylation process. Because of the cell and receptor specificity, a sugar chitosan composite is very useful for targeted drug delivery systems. Fucosylated chitosan and galactosylated chitosan are important for specific interaction with lectins and for targeting the delivery system to hepatocytes, respectively.

4.7 Chitosan and Methyl Acroloyl Glycine

A reaction between an amino group of chitosan and a carboxyl group of methyl acroloyl glycine (CS-MAG) produces a chitosan–methyl acroloyl conjugate. In comparison with crystalline chitosan, CS-MAG is an amorphous compound with lower intermolecular forces and thermal stability. The precursor

can be materialized via a photopolymerization technique in the presence of a photoinitiator.

4.8 Chitosan and 4-Azido-benzoic Acid

4-Azido-benzoic acid (Az-CS), with two functional groups (azide and carboxylic acid), is one of the crosslinking agents and photoinitiators. Photosensitive chitosan derivatives are formed by a reaction between a carboxylic acid group of benzoic acid and an amino group of chitosan. After ultraviolet (UV) irradiation, the azide functional group is changed into nitrene, crosslinked to form a gel-like structure [11].

5 Various Chitosan-Based Interpenetrating Polymer Network Hydrogels

5.1 Semi-interpenetrating Polymer Network of Chlorpheniramine Maleate

A semi-IPN of chitosan–glutamic acid beads is formed by crosslinking between glutaraldehyde and chitosan. The formation of chitosan–glutamic acid beads can be done by one two processes: (1) beads are prepared with the same weight ratio but varying amounts of crosslinker; or (2) beads of different weight ratios are prepared with a fixed amount of crosslinker. The swelling profile of the beads and the release rate of chlorpheniramine maleate (CPM) in different pH solutions have been studied, and CPM shows a greater degree of swelling in a basic medium than in an acidic medium. The rate of swelling of the matrix and the release of drugs are dependent on the degree of crosslinking, the weight ratio of chitosan–glutamic acid, and the pH of the solution. With variations in the weight ratio of chitosan–glutamic acid, the concentration of glutaraldehyde, and drug loading, the desired release rates can be achieved, which also helps in optimizing the drug-entrapping capacity and sustained release for an extended period of time. The outcomes also suggest that chitosan–glutamic acid crosslinked beads are suitable for controlled release of drugs. A viscous solution of chitosan–glutamic acid is prepared in 2% acetic acid solution and extruded to an alkali–methanol solution, and the precipitated beads are crosslinked using a glutaraldehyde solution [12].

5.2 Clarithromycin Interpenetrating Polymer Network Hydrogel

Clarithromycin IPN hydrogel is formed by chemical crosslinking between chitosan, polyvinyl pyrrolidine, and polyacrylic acid. A formulation with a greater quantity of chitosan showed greater swelling and drug release due to the presence of an NH_2

group, which ionizes at lower pH values. The results showed that IPN hydrogels exhibit greater swelling, mucoadhesion, and drug release at a lower pH value (pH 2), and are effective against *Helicobacter pylori* [13].

5.3 Metformin HCl Hydrogel

Hydrogels or polyelectrolyte systems are based on ionic crosslinking and are used as controlled-release dosage forms. These systems are based on the ability of their structure to entrap the drug within them. Metformin hydrochloride (MH) has been used as a model drug for this purpose. It is a highly water-soluble and low-permeability drug. Thus, development of a controllable dosage form system for controlled release of MH has been attempted. MH-loaded chitosan polyelectrolyte complex (PEC) hydrogel beads were prepared via ionotropic crosslinking with sodium tripolyphosphate (TPP). MH was dispersed in 1.5% glacial acetic acid and, with chitosan and polymers dispersed within it, was crosslinked with a 1% sodium tripolyphosphate solution adjusted to a pH of 6.0–6.4. The prepared beads were filtered and kept at 35 °C overnight to dry. The ratio of the polymer and drug combination was kept around 1:1. The particle shape, particle diameter, weight, percentage swelling, differential scanning calorimetry (DSC) findings, drug entrapment efficiency (DEE), and in vitro release were examined as physical and chemical characterization parameters of the resultant beads. The effects of incorporation of polymers such as sodium alginate, xanthan gum, hydroxypropyl methylcellulose, and hydroxyl ethylcellulose on the physicochemical properties of the beads were also studied. Spherical to oval beads with varying particle sizes, weights, DEEs, and sustained release profiles were obtained, depending on the polymer combination used. These beads were able to sustain the release of metformin HCl. In vitro dissolution studies were done to assess the release pattern of the drug from the beads over a 5- to 6-h period. The chitosan beads were subjected to stability studies for 1 month. The stability results for the chitosan beads after 1 month were shown to be favorable with respect to providing a possible controlled-release dosage form with the beads [14].

5.4 Repaglinide Semi-interpenetrating Polymer Network Hydrogel

A pH-sensitive chitosan/polyvinyl pyrrolidone (PVP)–based controlled drug release system for repaglinide has been studied. These hydrogels were obtained by crosslinking chitosan and PVP with glutaraldehyde to form a semi-interpenetrating polymer network (semi-IPN) and were characterized for their content uniformity, swelling index (SI), mucoadhesion, wettability, in vitro release, and release kinetics, which showed more than 95% loading of repaglinide and good swelling and mucoadhesion properties under acidic conditions. The swelling properties directly correlated with the protonation of a primary amino

group on chitosan. In an acidic medium, chitosan was ionized, and mucoadhesion occurred between the positively charged chitosan and the negatively charged mucus. In physiological medium conditions, less matrix swelling was noticed. The in vitro release profile revealed that the formulation containing chitosan (2% w/v) and PVP (4% w/v) in the ratio of 14:6 w/w provided complete drug release after 12 h. This release profile showed that all of the formulations followed a non-Fickian diffusion mechanism. The surface morphology of the semi-IPN was examined before and after dissolution in simulated gastric fluid (pH 1.2), which revealed generation of an open channel–like structure in the hydrogel after dissolution. The results also suggested that semi-IPNs of chitosan/PVP are good candidates for delivery of repaglinide in acidic environments [15].

5.5 Intelligent Semi-interpenetrating Polymer Network Chitosan–Polyethylene Glycol–Poly(Acrylamide) Hydrogel for Closed-Loop Insulin Delivery and Kinetic Modeling

An intelligent closed-loop insulin delivery system was developed for implantation with glucose-responsive semi-IPN hydrogels, which were synthesized from free radical polymerization of chitosan (CS), acrylamide (AAm), and polyethylene glycol (PEG). Immobilized glucose oxidase (GOx) and catalase (CAT), along with insulin, were loaded into the hydrogels to make an intelligent drug carrier capable of playing the role of an artificial pancreas. The glucose-responsive hydrogel acted as a self-regulating insulin delivery system, and the rate of insulin release was associated with the blood glucose level. Cell culture tests with fibroblast cells were conducted to perform biocompatibility testing for the drug carrier systems. The effects of the incorporated PEG on the swelling ratio (SR), drug loading capacity (DLC), and drug entrapment efficiency (DEE) of the intelligent semi-IPN hydrogels were evaluated using high-performance liquid chromatography (HPLC) and UV–visible spectroscopy. Optimization of the hydrogel was also investigated using a full factorial design and by changing the amount of PEG [16].

5.6 Hybrid pH-Sensitive Hydrogels of Chitosan-co-acrylic Acid for Controlled Release of Verapamil

Crosslinked hydrogels based on chitosan (CS) and acrylic acid (AA) were prepared by free radical polymerization with feed compositions using *N*,*N*-methylene-bis-acrylamide (MBA) as a crosslinking agent, with benzoyl peroxide used as a catalyst. The formation of hydrogel was done by electrostatic interaction between cationic groups in CS and anionic groups in AA. The formulated hydrogels were used for dynamic and equilibrium swelling studies. The swelling properties, the effect of pH, polymeric and monomeric compositions, and the degree of crosslinking were

investigated. Swelling studies were performed in USP phosphate buffer solutions with varying pH values of 1.2, 5.5, 6.5, and 7.5. The outcomes revealed that swelling was increased by an increase in the proportion of AA in the structure of the hydrogels in solutions with higher pH values. This was due to the presence of more carboxylic groups available for ionization. On the other hand, with an increase in the chitosan content, swelling increased in a solution of acidic pH, but this swelling was not significant, and it was due to ionization of amine groups present in the structure of the hydrogel. Swelling properties were decreased with an increase in the crosslinking ratio, owing to a tighter hydrogel structure. Porosity and the sol–gel fraction were also measured. With increases in CS and AA content, porosity and the gel fraction increased, whereas with an increase in MBA content, porosity decreased and the gel fraction increased. The Flory–Rehner theory was used to calculate the diffusion coefficient (D) and network parameters such as the average molecular weight between crosslinks (M_c), the polymer volume fraction in the swollen state (V_{2s}), the number of repeating units between crosslinks (M_r), and the crosslinking density (q). Selected samples were loaded with a model drug, verapamil. The release of verapamil depended on the ratio of CS to AA, the degree of crosslinking, and the pH of the medium. The release mechanisms were studied by fitting of the experimental data to model equations and calculation of the corresponding parameters. The outcomes revealed that the kinetics of drug release from the hydrogels in both pH 1.2 and pH 7.5 buffer solutions mainly followed non-Fickian diffusion [17].

5.7 pH-Sensitive Interpenetrating Network Hydrogels Based on Chitosan Derivatives and Alginate for Oral Drug Delivery

Methoxy polyethylene glycol–grafted carboxymethyl chitosan (mPEG-*g*-CMC) and alginate hydrogels were constructed as an IPN. mPEG-*g*-CMC hydrogel and mPEG were physically mixed with CMC hydrogel. Bovine serum albumin (BSA) was used as a model for a protein drug, which was encapsulated in the hydrogel network, and the drug release properties were studied. The hydrogels prepared by these two methods maintained good pH sensitivity; the loading capacity of the mPEG-*g*-CMC/alginate hydrogel was enhanced in comparison with that of the hydrogel prepared by physical mixing of mPEG. The burst release of the protein was slightly decreased at pH 1.2, while the release at pH 7.4 was improved and behaved like site-specific protein drug delivery in the intestine [18, 19].

5.8 Chitosan/Alginate Crosslinked Hydrogels: Preparation, Characterization, and Application for Cell Growth Purposes

A hybrid polymer network of chitosan was prepared with an alginate crosslinker using covalent linkage between two macromolecules. Fourier transform infrared (FTIR) spectroscopy and DSC were used as tools to characterize the structural and

thermal behavior of these hydrogels. Scanning electron microscopy (SEM) with an atomic force microscopy (AFM) attachment was used to investigate the morphological nature of the crosslinked material. A mixture of water and phosphate-buffered saline (PBS) solution was used to analyze the swelling properties of the gel. Hydrogel stability was provided by the presence of alginate in the chitosan/alginate hydrogel. In comparison with chitosan/alginate hydrogel prepared with 1 wt% DCC (*N*,*N*′-dicyclohexylcarbodiimide), the swelling of chitosan/alginate hydrogel prepared with 3 wt% DCC was limited. Hydrogels seeded with L929 mouse fibroblasts were used to measure the degree of cell proliferation. Chitosan/alginate hydrogels with 1 wt% DCC provided a better environment for cell attachment and cell proliferation. This study evaluated functional hydrogel formation by crosslinked chitosan and alginate as a novel biomaterial [20].

5.9 In Situ Formation of Chitosan–Gold Hybrid Hydrogel and Its Application for Drug Delivery

Chitosan and chloroauric acid in an aqueous medium were used to develop a novel chitosan–gold (CS–Au) hybrid hydrogel. Its physiochemical parameters – such as its UV absorption, structure, morphology, and swelling properties – were studied. The CS–Au hybrid hydrogel exhibited a marked water-absorbing property and was acclaimed as a drug delivery system for the anticancer drug doxorubicin (DOX) because of its high equilibrium water swelling property. The DLC and sustained drug release pattern correlated with the results of drug loading and release experiments. Moreover, DOX released from hydrogel, which itself had no cytotoxicity, showed biological activity similar to that of free DOX but with lower cytotoxicity due to its controllable release. These characteristics are ideal for a local drug delivery system, indicated that it has a promising potential future in the medical or pharmaceutical area [21, 22].

5.10 Hydrogels Made from Chitosan and Silver Nitrate

A gelation of chitosan solution with silver nitrate was developed to be an essential antibacterial agent. The critical concentration of chitosan (c*) was used as the rate-limiting step for continuous production of chitosan–silver hydrogel. At lower concentrations, the formation of nano- and microhydrogels was assessed. The swelling properties of hydrogels was assessed by sol–gel analysis. Also, the following tests were employed: (1) the hydrogels were tested mechanically; (2) the silver concentration was measured by inductively coupled plasma–optical emission spectroscopy (ICP-OES); (3) the morphology of the products was measured by SEM; and (4) the product formed at a low concentration of chitosan ($c < c^*$) was observed by dynamic light scattering (DLS) and UV–visible spectrophotometry. The obtained product was effective against *Escherichia coli* and *Bacillus subtilis* although the chitosan used in it showed no such activity [23].

5.11 Interpenetrating Polymer Network Hydrogels of Chitosan and Poly(2-Hydroxyethyl Methacrylate) for Controlled Release of Quetiapine

Interpenetrating polymer networks of chitosan and 2-hydroxyethyl methacrylate (HEMA) have been produced. pH was used as a limiting parameter to study the swelling properties and chitosan content of the network. At approximately 98 °C and 155 °C, two transitions were shown, which corresponded to the networks of pHEMA and chitosan, respectively, as per the DSC studies, and demonstrated that the obtained materials were amorphous and interpenetrated. The viscoelastic behavior of the materials was studied by creep recovery and stress relaxation studies. Quetiapine was used as a model drug to study controlled-release behavior, and it was found that the process was controlled by diffusion and by relaxation of the polymer network. Lysozyme enzyme was used to quantify the degradation of materials under simulated physiological conditions. An increase in the chitosan content directly correlated with the degree of degradation [24–26].

5.12 Production of Chitosan-Based Hydrogels for Biomedical Applications

Chitosan-based hydrogel is produced by hydrophilic reactions of polar functionalities such as amino and OH groups. Chitosan hydrogels are capable of absorbing large quantities of water without changes in structural features. Using a variety of strategies based on ionic, polyelectrolyte, chemical modification, and interpenetrating network techniques, chitosan-based hydrogels have been designed and investigated to deliver therapeutics to the site of action in a controlled-release manner. Micro- and nanosized configurations of chitosan-based hydrogel have shown immense applications in biomedical areas such as drug delivery, wound healing, and tissue engineering [27].

5.13 Interpenetrating Polymer Network Hydrogel Microspheres for Oral Controlled-Release Applications

Sodium carboxymethyl cellulose (Na-CMC) and polyvinyl alcohol (PVA) interpenetrating polymer network hydrogel microspheres were prepared by a water-in-oil (w/o) emulsion crosslinking method for an oral controlled-release drug delivery system for the nonsteroidal anti-inflammatory drug diclofenac sodium (DS). The microspheres were prepared with variation in the ratios of Na-CMC to PVA with constant percentage drug loading and extent of crosslinking density at polymer weight. SEM was used to identify loose and rigid surfaces of microspheres. The structure of the IPN was justified by FTIR spectroscopy and x-ray diffraction (XRD) analysis. The dispersive nature of the encapsulated drug was estimated by

DSC analysis. The in vitro drug release study was evaluated depending on the acid and alkaline media. All formulations exhibited satisfactory physicochemical and in vitro release characteristics. The release data indicated a non-Fickian diffusion mechanism of drug release from the formulations. Thus, the study revealed that DS-loaded IPN microspheres are suitable for oral controlled-release application [28].

5.14 Synthesis of a Novel Interpenetrating Polymer Network Hydrogel as a Drug Delivery System

Novel IPN hydrogels of chitosan with poly(acrylic acid) were developed for controlled release of an amphetamine drug by use of simultaneous polymerization/crosslinking of an acrylic acid monomer in the presence of chitosan and a crosslinker. Variation in the composition of the IPN was achieved by variation in the concentration of the crosslinker. The characterization of the IPN in terms of pH-sensitive behavior was calculated by equilibrium swelling studies, which revealed that the release of amphetamine was much higher at pH 7.4 than at pH 1.2, which indicated that the release system was controlled and could be used as a release system for intestine-specific drug delivery [29, 30].

5.15 Sterculia Gum–Based Hydrogels for Drug Delivery Applications

Sterculia gum is one of the medicinally important plant-derived water-soluble polysaccharides obtained from the exudate of the tree *Sterculia urens* (family: Sterculiaceae). It was identified as a promising biodegradable material in the development of various biomedical applications, including drug delivery applications and wound dressing applications. Sterculia gum has also been employed as an excipient in the design of various pharmaceutical applications. In recent years, several attempts at modification of sterculia gum have been undertaken to develop sterculia gum–based hydrogels for controlling the rate of hydration and swelling, and also for tailoring the release profile of various types of drug. In the development of these sterculia gum–based hydrogels, modifications of sterculia gum through polymer blending, crosslinking, IPN formation, polymer grafting, etc., were investigated for improved drug delivery applications. Most of these previously reported sterculia gum–based hydrogels have been found to be effective for gastroretentive deliveries as wound dressings for sustained release of various drugs. This chapter provides a comprehensive and useful discussion on previously investigated sterculia gum–based hydrogels for use in drug delivery applications, describing the source, composition, and properties of sterculia gum, and discussing the formulations of various sterculia gum–based hydrogel systems used in various types of drug delivery application [31, 32].

5.16 Chitosan/Gelatin Membranes Using Chitosan Hydrogel

As we know, chitin and chitosan are novel biomaterials. In this work a suspension of chitosan hydrogel was mixed with gelatin to develop novel chitosan/gelatin membranes, which were characterized by SEM, XRD, mechanical, swelling, and thermal studies. The XRD data revealed homogeneous and smooth morphology of the chitosan/gelatin membranes, as well as showing good compatibility and interaction between the chitosan and gelatin. In wet conditions with a chitosan to gelatin mixture ratio of 0.5, stress and elongation of the chitosan/gelatin membranes were revealed, along with good swelling, mechanical, and thermal properties. Cell adhesion studies were also carried out, using human MG-63 osteoblast–like cells to quantify cell adhesion, in which cells were incubated with chitosan/gelatin membranes for 24 h to confirm the cell adhesion. The prepared chitosan/gelatin membranes were biologically active and were suitable for cell adhesion, which was an important criterion for tissue engineering [33].

5.17 Chitosan/Polyacrylonitrile Semi-interpenetrating Polymer Network Hydrogel

In one study a chitosan/polyacrylonitrile semi-IPN hydrogel system was formed, based on various blends of chitosan/polyacrylonitrile polymer. Crosslinking of chitosan via glutaraldehyde vapors was utilized to develop a semi-IPN, and DSC, FTIR, and field emission (FE)-SEM were used as tools to reflect the microstructures of the hydrogels. DSC thermograms of the hydrogel blends showed a single *T*g value (at 179–152 °C for Gel1–Gel4), which confirmed good miscibility between the two polymers. For a semi-IPN (Gel7) the *T*g appeared at slightly lower temperature (128 °C) than previously, which also suggested reduced intermolecular interactions between the two polymers being observed because of crosslinking of the chitosan. The FTIR data revealed no change in the characteristic band positions of the two polymers for the hydrogel blends (Gel1–Gel4) and also a characteristic doublet at 1563 cm^{-1} and 1630 cm^{-1}, which confirmed crosslinking of chitosan with glutaraldehyde to form a semi-IPN hydrogel (Gel7). The FE-SEM images showed a homogenous surface (with no phase separation) and cross-sectional morphologies for the blend hydrogels (Gel1–Gel4) and semi-IPN hydrogel (Gel7). The percentage swelling was suggested to decrease with a simultaneous increase in stability as the crosslinking time was increased. The semi-IPN hydrogel (Gel7) showed improved stability and fair swelling. The potential of the blend hydrogel (Gel1) and semi-IPN hydrogel (Gel7) as adsorbents was studied using rhodamine B dye as an indicator. A significant adsorption affinity for rhodamine B dye was shown in the case of the semi-IPN hydrogel (Gel7). The outcomes best fitted pseudo-second-order kinetics and a Langmuir isotherm. An intraparticle diffusion model was used to confirm diffusion as the only rate-limiting step [34].

5.18 Semi-interpenetrating Polymer Network Superabsorbent Chitosan–Starch Hydrogel

In this study, a semi-IPN superabsorbent chitosan–starch (ChS) hydrogel was used to efficiently remove Direct Red 80 (DR80) dye from the aqueous phase. The effects of the initial pH, ChS dose, initial dye concentration, temperature, and salts on the sorption of DR80 dye were evaluated. A maximum swelling capacity of 15 g/g was shown in the case of the ChS hydrogel. The sorption equilibrium data revealed good agreement with a Freundlich isotherm, which also best fitted a pseudo-second-order kinetic model. The maximum uptake capacity and mean sorption energy of the hydrogel (312.77 mg/g and E = 11.34–14.9 kJ/mol) revealed that the sorption nature of DR80 was mainly of a chemisorption type. The spontaneous endothermic data of the sorption process correlated with the temperature dependency data, which were also favorable at a higher temperature on the basis of the enthalpy value (H° = +83.68 kJ/mol). Intraparticle diffusion data according to the Boyd model were used as a limiting step for DR80 uptake and, finally, sorption/desorption studies were performed to investigate the reusability of the ChS hydrogel, which demonstrated significant sorption for four consecutive cycles [35].

5.19 Glucose-Sensitive Antibacterial Chitosan–Polyethylene Oxide Hydrogel

This works reflects the development of a novel glucose-sensitive chitosan–polyethylene oxide (CS/Polyethylene oxide = 1:0.5–1:2.5) hydrogel for controlled release of metronidazole (MNZ) by use of chemical crosslinking and immobilization of the glucose oxidase (GOx) process. FTIR spectroscopy, compressive mechanical testing, rheological analysis, cytotoxicity testing, and antibacterial testing against *Porphyromonas gingivalis* were used as characterization tools for the hydrogel. The CS-Polyethylene oxide composite hydrogel possessed more significant mechanical properties and biocompatibility than a single-component hydrogel, which might have been the result of physical crosslinking and formation of a semi-IPN. This novel hydrogel has a unique self-regulating ability to release MNZ, depending on the response to the environmental glucose stimulus. It mainly releases more drugs at a higher glucose concentration that can be correlated with its ability to inhibit *P. gingivalis*. This study produced the glucose-sensitive antibacterial hydrogel as a new therapeutic material for treatment or prevention of periodontitis in diabetic patients [36–38].

5.20 Granular Semi-interpenetrating Polymer Network Hydrogel Based on Chitosan and Gelatin for Fast and Efficient Adsorption of Cu^{2+} Ions

In situ novel granular semi-IPN hydrogels were prepared in an aqueous solution by free radical grafting and crosslinking using chitosan (CTS), acrylic acid (AA),

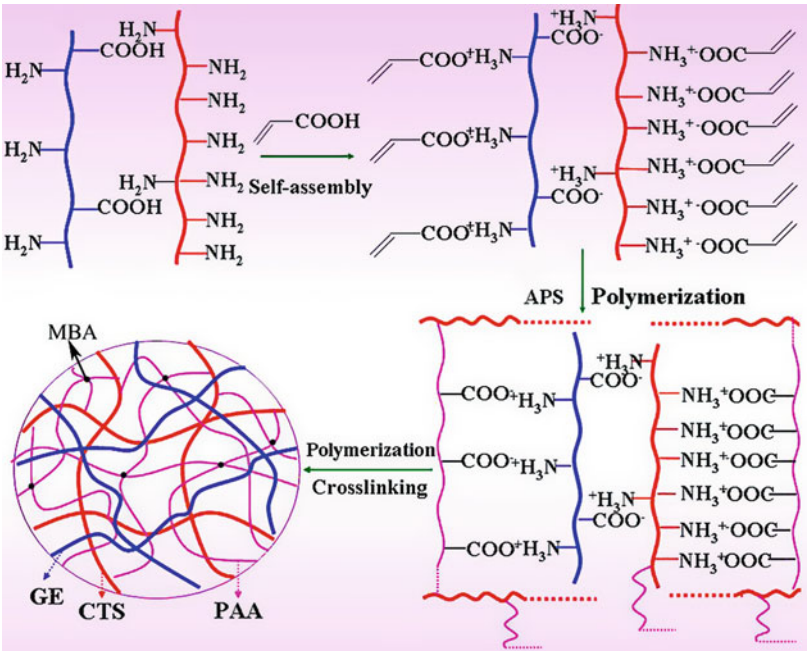


Fig. 3 Granular chitosan-*g*-poly(acrylic acid)/gelatin (CTS-*g*-PAA/GE) semi-interpenetrating polymer network hydrogel. (Reproduced from Wen et al. [39], copyright © 2013, with permission from Elsevier BV)

gelatin (GE), and MBA. FTIR spectra and elemental analysis were used as tools to confirm the grafting of AA monomers onto a CTS backbone, and the GE macromolecular chains were interpenetrated through the chitosan-*g*-poly(acrylic acid) (CTS-*g*-PAA) network. As per the SEM observations, the hydrogels were granular in nature and composed of numerous microspheres. The gel strength, adsorption, reuse, and recovery properties of the hydrogels for Cu^{2+} ions were thoroughly investigated. The outcomes indicated that the hydrogel with 2 wt% GE had the highest adsorption capacity of 261.08 mg/g, with a recovery ratio of 95.2%. Incorporation of 10 wt% GE enhanced the storage modulus by 103.4% ($\omega = 100$ rad/s) and 115.1% ($\omega = 0.1$ rad/s) and the adsorption rate by 5.67%. The adsorption capacity of the hydrogel was still as high as 153.9 mg/g after five cycles of adsorption–desorption, which correlated with the ion exchange and complexation interactions between the functional groups (-COO and $-NH_2$) of the hydrogels and the Cu^{2+} ions being the predominant adsorption mechanisms [39]. Figure 3 shows the structural formation of the granular CTS-*g*-PAA/GE semi-IPN hydrogel. Figure 4 shows SEM images of the semi-IPN hydrogel. Table 1 lists the adsorption isotherm parameters for the adsorption of Cu^{2+} ions onto the hydrogels.

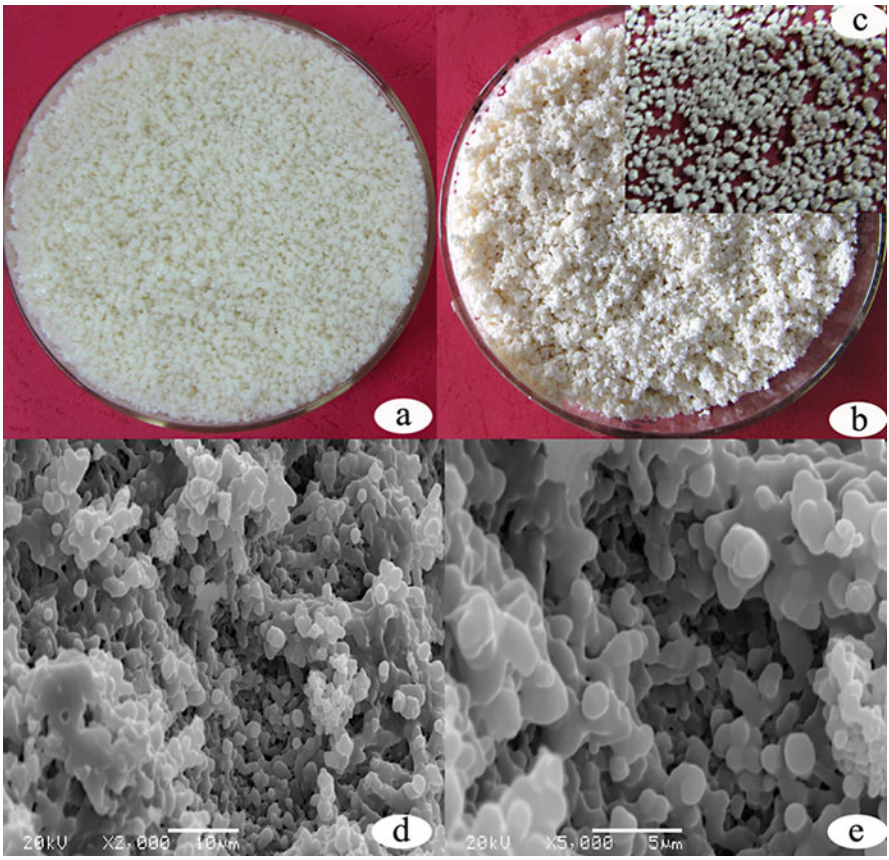


Fig. 4 Formed semi-interpenetrating polymer network (IPN) hydrogel before dewatering (**a**), after dewatering by methanol (**b**), and after drying (**c**). Scanning electron micrographs of semi-IPN10 hydrogel at magnifications of ×2000 (**d**) and ×5000 (**e**). (Reproduced from Wen et al. [39], copyright © 2013, with permission from Elsevier BV)

5.21 Semi-interpenetrating Polymer Network Hydrogel: Preparation, Swelling Properties, and Adsorption Studies of Co (II)

Superadsorbent semi-IPN hydrogels of polyvinyl alcohol/poly(acrylic acid-co-acrylic amide) (PVA-P(AA-co-AM)) were developed via a free radical polymerization method under ultrasound-assisted conditions. The reaction conditions were optimized by L16 (45) orthogonal experiments, and the formation of hydrogels was characterized by FTIR, SEM, and thermogravimetric analysis (TGA) studies. In various pH and saline solutions, the swelling properties of hydrogels were observed. The pH of the solution showed an obvious influence on the swelling characteristics of the hydrogel, and the salt resistance was greater in low valency of the salt solution relative to high valency.

Table 1 Estimated adsorption isotherm parameters for adsorption of Cu^{2+} ion onto hydrogels. (Reproduced from Wen et al. [39], copyright © 2013, with permission from Elsevier BV)

	Langmuir equation			Freundlich equation		
Sample	q_m	b	R^2	K	n	R^2
CTS-*g*-PAA	300.31	0.0356	0.9998	52.36	3.7543	0.9195
Semi-IPN2	305.82	0.0486	0.9999	61.65	4.0514	0.9259
Semi-IPN10	294.13	0.0271	0.9997	48.19	3.6784	0.9275
Semi-IPN20	277.04	0.0244	0.9996	43.36	3.6129	0.9246

CTS-g-PAA chitosan-*g*-poly(acrylic acid), *IPN* interpenetrating polymer network

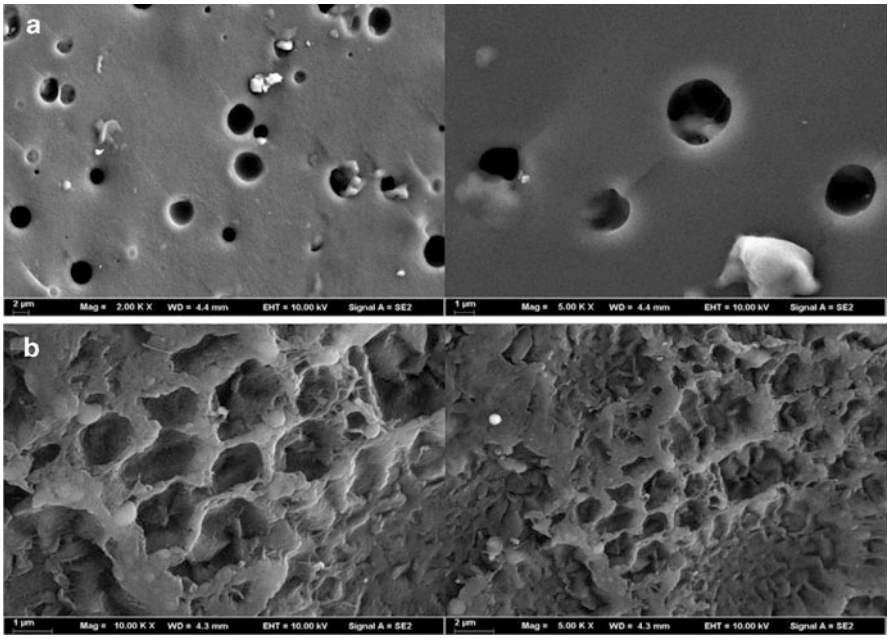


Fig. 5 Scanning electron microscopy images showing different magnifications of poly(acrylic acid-co-acrylic amide) (P(AA-co-AM)) (**a**) and sodium lignosulfonate–grafted poly(acrylic acid-co-acryl amide)-17 (SL-P(AA-co-AM)-17) (**b**). (Reproduced from Xiaohong et al. [40], copyright © 2016, with permission from Elsevier BV)

Also, the swelling behavior was evaluated in an aqueous solution, which revealed that the swelling process maintained the Schott model and non-Fickian diffusion properties. The optimum adsorption of cobalt (II) ions from aqueous solutions was observed at a pH value close to 4, and adsorption kinetics and adsorption isotherms for cobalt (II) were maintained with the pseudo-second-order model and the Freundlich model, respectively. Finally, it was concluded that the adsorption behavior was spontaneous and endothermic [40]. Figure 5 shows SEM images of P(AA-co-AM) and sodium lignosulfonate–grafted poly(acrylic acid-co-acryl amide)-17 (SL-P(AA-co-AM)-17). Table 2 compares the Co (II) adsorption capacities of some adsorbents.

Table 2 Comparison of Co (II) adsorption capacities of some adsorbents. (Reproduced from Xiaohong et al. [40], copyright © 2016, with permission from Elsevier BV)

Adsorbent	Adsorption capacity (mg g^{-1})	Concentration of Co ions (mg L^{-1})
Acacia nilotica leaf carbon	12.8	50
Modified chelating fibers	72.88	350
Crosslinked magnetic CSIS	53.51	350
Crosslinked magnetic CSMO	60.15	350
Nanostructured goethite	86.6	500
γ-MnO_2 nanostructure	90.91	500
Apricot stone activated carbon	16.3	80
Nano-NaX geolite	125.3	400
Chitosan–montmorillonite	150	270
PVA-P (AA-co-AM)	184 (a), 332 (b)	250 (a), 400 (b)

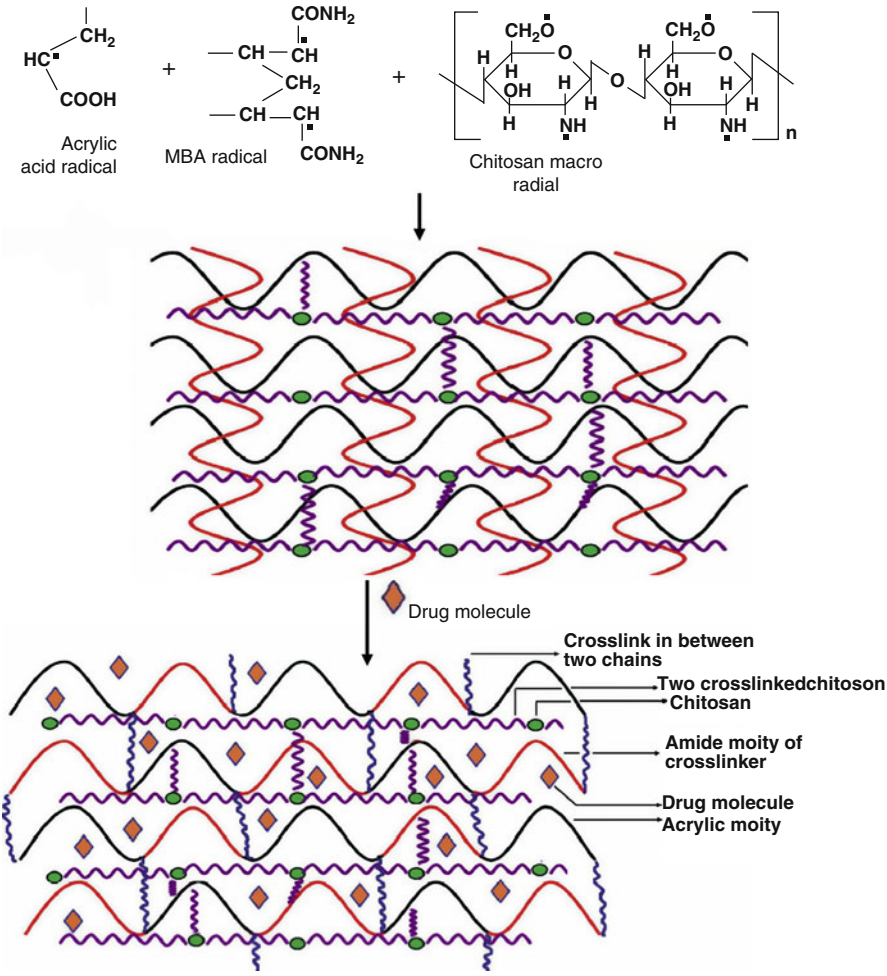
CSIS chitosan–isatin Schiff's base resin, *CSMO* chitosan–diacetylmonoxime Schiff's base resin, *PVA-P(AA-co-AM)* polyvinyl alcohol/poly(acrylic acid-co-acrylic amide)

5.22 Interpenetrating Polymer Network Hydrogel Membrane of Poly(*N*-Isopropylacrylamide)/Carboxymethyl Chitosan

A poly(*N*-isopropylacrylamide)/carboxymethyl chitosan ((PNIPAAm)/(CMCS)) interpenetrating hydrogel was prepared, and the effects of the feed ratio of components, swelling medium and irradiation dose on the swelling and deswelling properties of the hydrogel were studied in detail. The outcomes revealed that the introduction of CMCS did not shift the lower critical solution temperature (LCST) (at 32 °C), which was similar to that of pure PNIPAAm. At pH 2, the lowest swelling ratio was observed. The thermosensitivity and pH sensitivity of the IPN hydrogel depended on the irradiation dose; the swelling ratio was decreased with an increasing dose. The ratio of PNIPAAm: CMCS with 1:4 w/w hydrogel was not thermosensitive in distilled water, whereas a discontinuous volume phase transition occurred in pH 2 buffer and a continuous transition was observed in pH 8 buffer. Consequently, a combination of pH and temperature might be coupled to control the responsive behavior of these hydrogels [41].

5.23 Controlled Release of Tinidazole and Theophylline from Chitosan-Based Composite Hydrogels

Free radical crosslink copolymerization of acrylic acid (AA) and *N*-methylene-bis-acrylamide (MBA) in the presence of chitosan (CS) was used to synthesize various composite hydrogels. During polymerization, CS was incorporated in situ in the crosslinked polyacrylic acid gel to obtain composite



Scheme 1 Formation of composite hydrogel. (Reproduced from Himadri et al. [42], copyright © 2014, with permission from Elsevier)

hydrogels. FTIR, 13C nuclear magnetic resonance (NMR), differential thermal analysis (DTA), TGA, XRD, swelling and diffusion characteristics, and network parameters were used to identify the structure and properties of the hydrogels. Tinidazole and theophylline were used as model drugs with these hydrogels to evaluate loading and in vitro release behaviors. The drug release behavior from the gels was strongly influenced by the wt% of CS and MBA and the pH of the medium. The release rate of these two drugs was much faster at pH 7.6 than at pH 1.5 [42]. Scheme 1 represents the formation of the composite hydrogel. Table 3 lists the swelling diffusion and network parameters of the hydrogels.

Table 3 Swelling diffusion and network parameters of hydrogels. (Reproduced from Himadri et al. [42], copyright © 2014, with permission from Elsevier)

Polymer	k_{s2}/r_0[a]	ESR_{expt}/ ESR_{cal} (g/g)	$r^2/X^2/F$	$k_D/n/$ $D \times 10^{5a}$	$r^2/X^2/F$	$M_c \times 10^{-6}/$ $\rho_c \times 10^{-17}/$ ς
MBA 1	0.001931/0.0323	13.06/14.84	0.96/ 0.0.449/ 910	0.018/ 0.57/2.5	0.963/ 0.0008/ 3363	21/0.53/ 916
MBA 2	0.0022/0.019	8.39/8.911	0.993/ 0.294/ 1365	0.041/ 0.39/ 1.81	0.990/ 0.0011/ 1920	3.3/4.14/ 812
MBA 3	0.009101/0.0705	6.32/5.46	0.937/ 0.169/ 1238	0.143/ 0.27/ 4.58	0.987/ 0.0009/ 5882	7.46/3.52/ 416
I 1.0	0.0025/0.0174	7.073/8.190	0.996/ 0.063/ 1885	0.038/ 0.42/ 3.32	0.951/ 0.0018/ 474	3.1/10.81/ 341
I 0.75	0.0023/0.028	11.3/12.56	0.986/ 0.610/ 280	0.043/ 0.38/ 2.23	0.998/ 0.0013/ 1779	3.2/5.52/ 417
I 0.5	0.0022/0.019	8.39/8.911	0.993/ 0.294/ 1365	0.041/ 0.39/ 1.81	0.990/ 0.0011/ 1920	3.3/4.14/ 812
I 0.25	0.0048/0.038	7.252/7.87	0.953/ 0.038/ 3029	0.148/ 0.28/ 1.84	0.9675/ 0.002/ 379	3.73/2.7/ 1261
CS 0.50	0.001790/0.029	13.157/14.47	0.992/ 0.132/ 4906	0.018/ 0.56/ 3.50	0.995/ 0.0014/ 5398	3.78/2.1/ 846
CS 1.0	0.001398/0.0295	16.32/19.74	0.996/ 0.306/ 3723	0.011/ 0.63/ 4.53	0.998/ 0.0042/ 1979	6.2/1.62/ 854
CS 2.0	0.001013/0.013	7.18/8.94	0.972/ 0.12/ 1423	0.012/ 0.62/ 1.18	0.908/ 0.0036/ 1746	1.38/2.4/ 421
AA 15	0.0020/0.0382	6.112/7.765	0.952/ 0.21/ 406	0.023/ 0.53/5.6	0.955/ 0.013/ 108	6.23/1.62/ 378
AA 20	0.0013/0.0201	7.433/8.16	0.986/ 0.80/ 423	0.013/ 0.63/ 7.91	0.988/ 0.002/ 829	10/0.8/817
AA 25	0.0022/0.019	8.39/8.911	0.993/ 0.294/ 1365	0.041/ 0.39/ 1.81	0.990/ 0.0011/ 1920	3.3/4.14/ 812

AA acrylic acid, *CS* chitosan, *MBA N*-methylene-bis-acrylamide

[a] k_{s2} (g gel/g water min), r_0 (g water/g gel min), k_D, n, D (cm^2/s)

5.24 Chitosan-Poly(*N*-Isopropylacrylamide) Full Interpenetrating Polymer Network Hydrogels

Chemical amalgamation of a methylene bis-acrylamide (MBAM) crosslinked poly (*N*-isopropylacrylamide (PNIPAM) network with a formaldehyde (HCHO) crosslinked CS network was used to develop full IPN chitosan/poly(*N*-isopropylacrylamide) (CS/PNIPAM) hydrogels. The extractability of PNIPAM within the gel, the phase transition behavior, the swelling dynamics in the aqueous phase, and the swelling behavior in ethanol/water mixtures were evaluated, and the microstructure was quite different from those of the semi-IPN CS/PNIPAM hydrogels, in which PNIPAM was simply embedded. Like the semi-IPN CS/PNIPAM hydrogels, however, the newly formed gel was temperature sensitive; it was transparent below 30 °C and opaque above that temperature. It was expected that the new smart hydrogels may find uses in separation science and also in the design and preparation of new soft machines [43]. Figure 6 shows general surface views of various xerogels. Figure 7 shows plots of the swelling ratio against the swelling time for the two CS/PNIPAM gels at two different temperatures.

5.25 Dual Crosslinked Iminoboronate–Chitosan Hydrogels

Chitosan-based hydrogels have been extensively studied in biomedical, industrial, and environmental applications, but their biomedical use has been limited by the toxicity of different organic crosslinkers. To overcome this limitation, a new strategy to produce supramolecular chitosan hydrogels has been devised using low molecular weight compounds, which are able to form covalent linkages and H-bonds to give

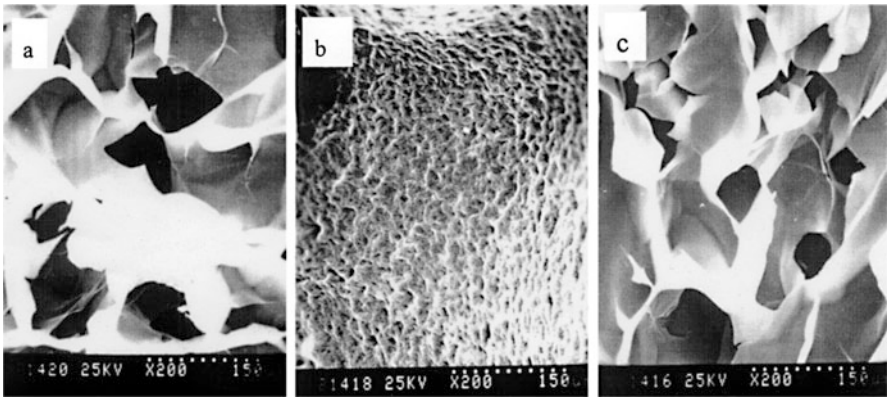


Fig. 6 General surface view of various xerogels. (**a**) Chitosan (CS). (**b**) Semi-interpenetrating polymer network (IPN) CS/poly(*N*-isopropylacrylamide) (PNIPAM). (**c**) Full IPN CS/PNIPAM. (Reproduced from Mingzhen et al. [43], copyright © 2001, with permission from Elsevier BV)

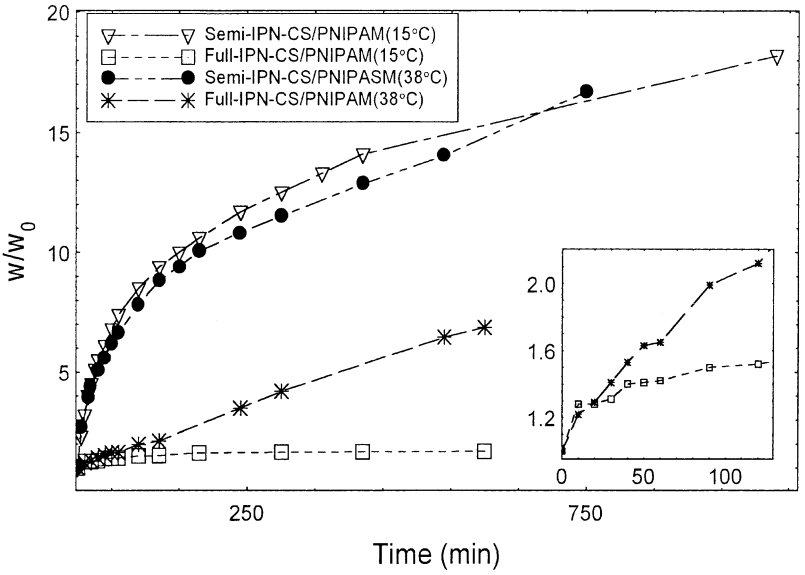
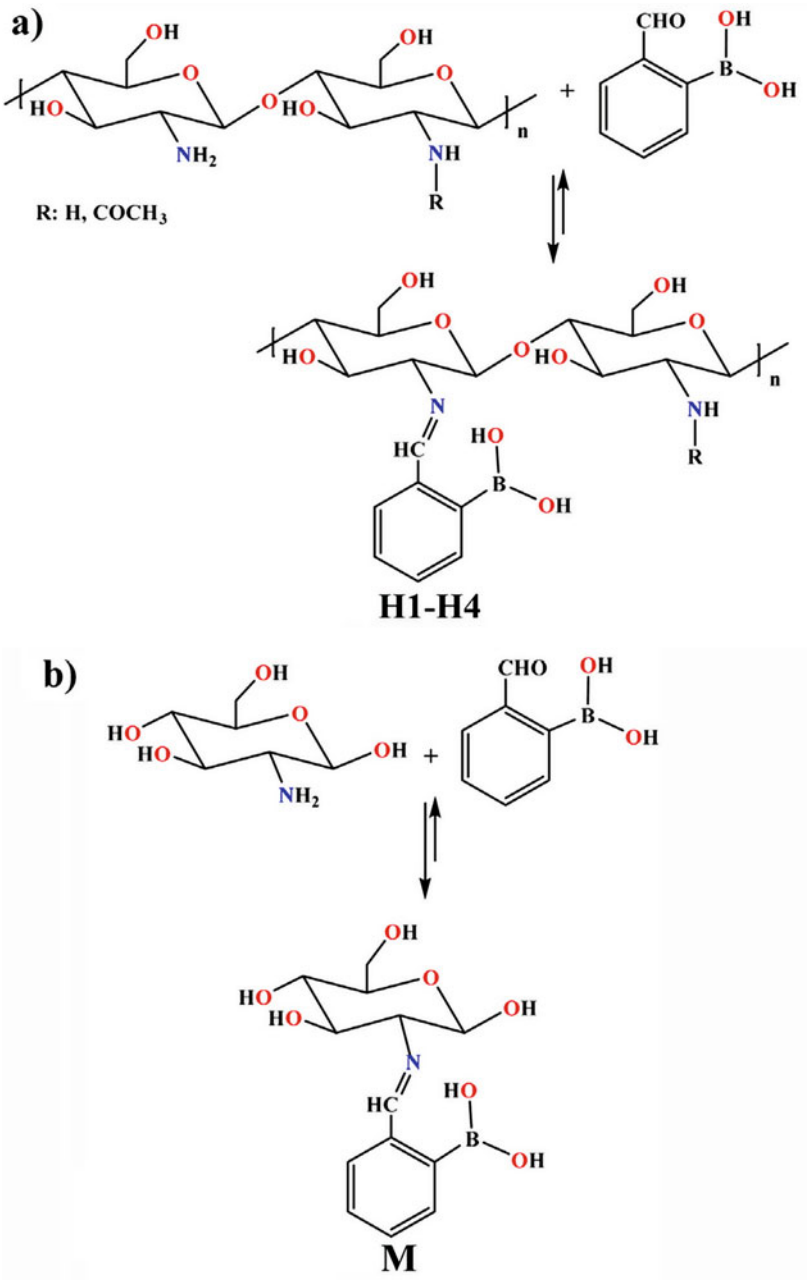


Fig. 7 Plots of the swelling ratio against the swelling time for two chitosan/poly(*N*-isopropylacrylamide) (CS/PNIPAM) gels at two different temperatures. (Reproduced from Mingzhen et al. [43], copyright © 2001, with permission from Elsevier BV)

dual crosslinking hydrogels. To fulfill this purpose, 2-formyl phenylboronic acid was used, which incorporates imine stabilization via iminoboronate formation and has potential antifungal activity due to the presence of boric acid residue. Chemophysical crosslinking using a dual iminoboronate–chitosan network was used to form hydrogels, as indicated by FTIR and NMR spectroscopy. Further, XRD studies also demonstrated three-dimensional nanostructuring of the iminoboronate network with consequences for the micrometer-scale morphology and improvement of mechanical properties, evaluated by SEM and rheological investigation. The hydrogels showed strong inhibitory activity against *Candida* planktonic yeasts and biofilms, showing promise as a treatment for recurrent vulvovaginitis infections [44]. Scheme 2 shows the obtaining of the hydrogels and the model compound. Figure 8a shows representative XRD of the iminoboronate–chitosan xerogels and the chitosan reference. Figure 8b shows a schematic representation of an iminoboronate–chitosan cluster.

5.26 Ring-Like Structured Chitosan–Metal Hydrogel

To improve the adsorbent ability and facilitate the solid/liquid separation of chitosan, its structure was molded into several shapes. A ring-like structure of chitosan had a relatively large surface area and high chemical accessibility; the characteristics of its plate-like counterparts have not yet been reported. In this



Scheme 2 Obtaining of the hydrogels and the model compound. (Reproduced from Daniela et al. [44], copyright © 2016, with permission from Elsevier Ltd.)

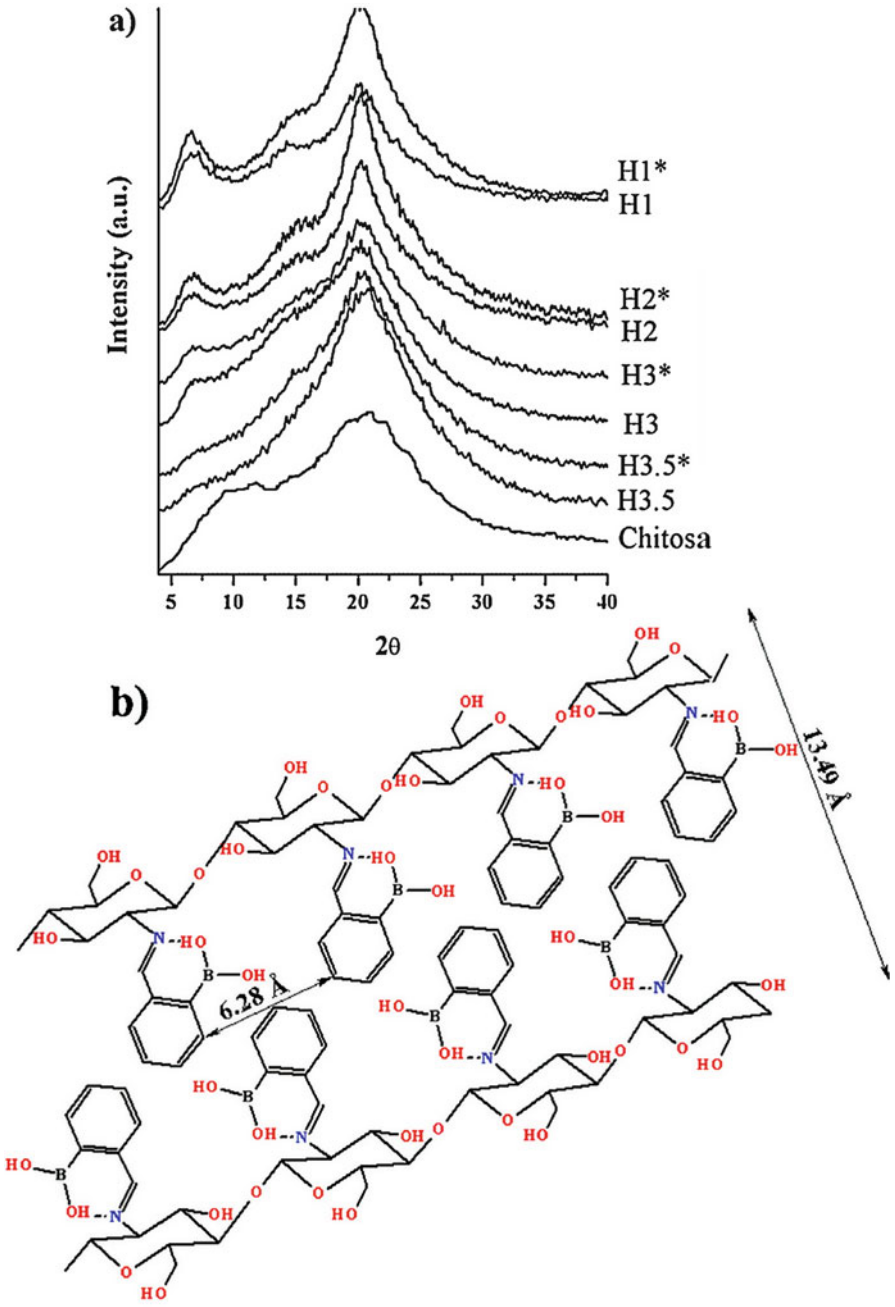


Fig. 8 (**a**) Representative x-ray diffraction of iminoboronate–chitosan xerogels and chitosan reference. (**b**) Schematic representation of an iminoboronate–chitosan cluster. (Reproduced from Daniela et al. [44], copyright © 2016, with permission from Elsevier Ltd.)

Scheme 3 Schematic illustration of the transition of chitosan hydrogel in the deposition process. (Reproduced from Hao et al. [45], copyright © 2016, with permission from Elsevier Inc.)

work, a novel concept was fabricated to form a highly efficient ring-like chitosan hydrogel structure via a sulfate ionic crosslinking method, and its mass production and formation mechanism were fully proposed. A ring-like chitosan–Fe(III) hydrogel exhibited outstanding adsorbent properties with an AR73 removal rate of 98.53% and a Cr(VI) removal rate of 90.53%. The adsorption of AR73 fitted well with the pseudo-second-order model and Langmuir isotherm model, which indicated that the chitosan–Fe(III) hydrogel ring structure possessed a considerable adsorption capacity of 205.2 mg/g. Also, the chitosan–Fe (III) hydrogel ring could efficiently adsorb both AR73 and Cr(VI) simultaneously (96.9% and 85.9%, respectively). Overall, this study revealed a facile method to prepare ring-like structures of chitosan–metal hydrogel, which could be mass-produced as multifunctional materials for practical applications [45]. Scheme 3 shows a schematic illustration of the transition of chitosan hydrogel in the deposition process. Figure 9 shows chitosan hydrogels with the addition of different kinds of metal salt.

5.27 Carboxymethyl Chitosan/ZnO Nanocomposite Hydrogels

Carboxymethyl chitosan/ZnO nanocomposite hydrogels were successfully prepared via in situ formation of ZnO nanorods in a crosslinked carboxymethyl chitosan (CMCh) matrix by connection of the CMCh hydrogel matrix with zinc nitrate solution followed by oxidation of zinc ions in an alkaline media. FTIR spectroscopy, XRD, and SEM were used as tools to characterize the CMCh/ZnO hydrogels. SEM revealed data on the ZnO nanorods in the hydrogel matrix, with the size ranging from 190 nm to 600 nm. In different pH media, the swelling behavior of the prepared nanocomposite hydrogels was evaluated. The CMCh/ZnO nanocomposite hydrogel showed greater swelling properties in different pH solutions than the neat CMCh hydrogel. Furthermore, the antibacterial activity of the CMCh/ZnO hydrogel against *E. coli* and *Staphylococcus aureus* was studied. An excellent antibacterial effect revealed the importance of the development of CMCh/ZnO nanocomposite hydrogel [46, 47].

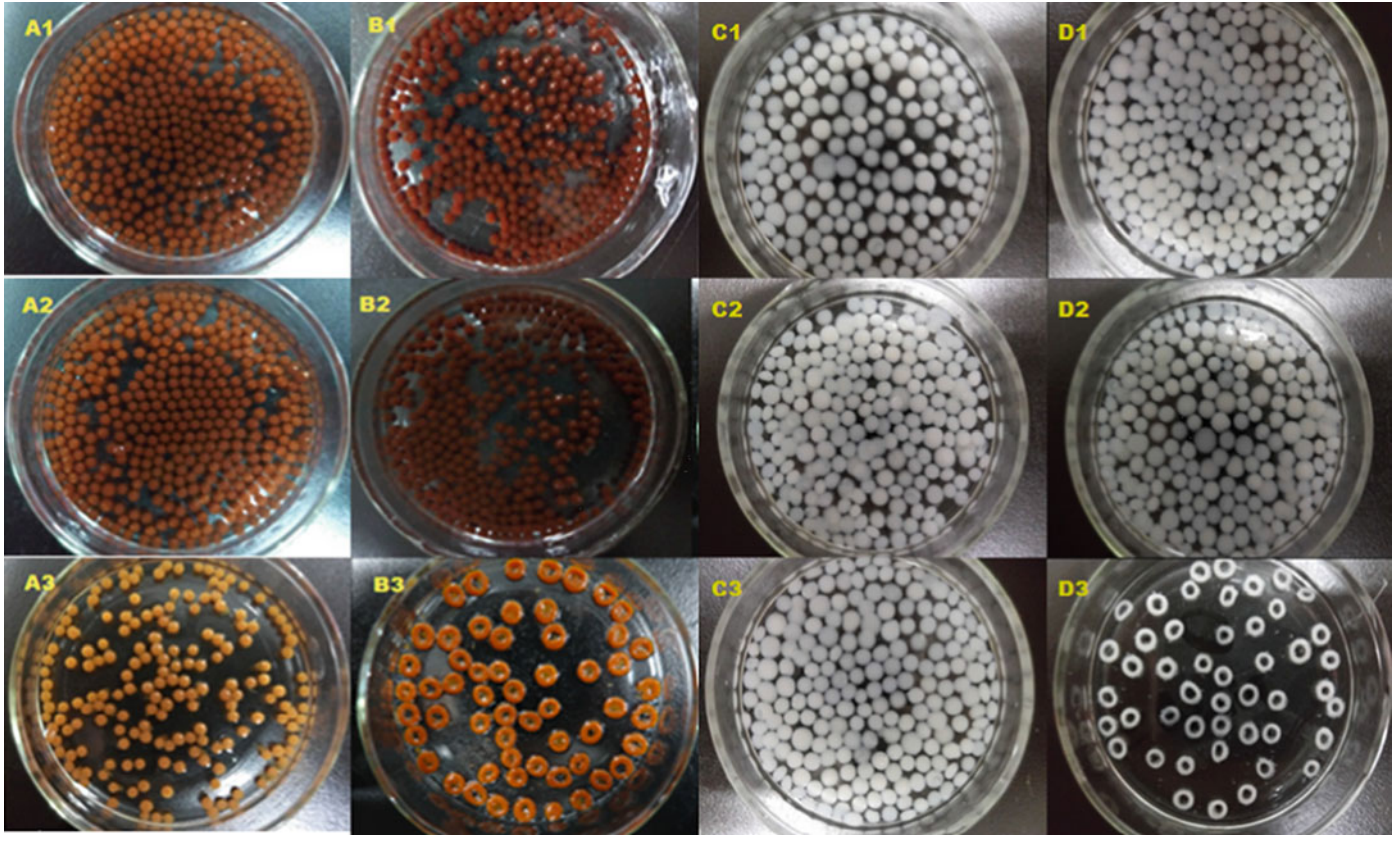


Fig. 9 Chitosan hydrogel with addition of different kinds of metal salt. **a1** $FeCl_3$, **a2** $Fe(NO_3)_3$, and **a3** $Fe_2(SO_4)_3$ at a low concentration. **b1** $FeCl_3$, **b2** $Fe(NO_3)_3$, and **b3** $Fe_2(SO_4)_3$ at a high concentration. **c1** NaCl, **c2** $NaNO_3$, and **c3** Na_2SO_4 at a low concentration. **d1** NaCl, **d2** $NaNO_3$, and **d3** Na_2SO_4 at a high concentration. (Reproduced from Hao et al. [45], copyright © 2016, with permission from Elsevier Inc.)

5.28 Thyroxine-Releasing Chitosan/Collagen–Based Smart Hydrogels

In one study, new porous thyroxine-containing proangiogenic hydrogels were developed via a freeze gelation protocol. FTIR spectroscopic analysis was used to investigate the chemical structure of the synthesized hydrogels. SEM was used to analyze the morphology and pore dimensions of the hydrogels. A 10-μg thyroxine-loaded hydrogel (TLH-10) showed a greater degree of swelling than a 1-μg thyroxine-loaded hydrogel (TLH-1) and a control. Three different media – PBS, lysozyme, and hydrogen peroxide – were used to study the degradation of hydrogels, and relatively higher degradation was seen in hydrogen peroxide. Chick chorioallantoic membrane was used to check the angiogenic potential of the synthesized materials. The TLH-1 hydrogel stimulated angiogenesis more than TLH-10, and blood vessels were attached and very much grown into the scaffold [48].

5.29 Mucoadhesive Chitosan Hydrogels for Rectal Drug Delivery

Mucoadhesive drug delivery systems are mainly stuck on mucosal tissues and prolong the local retention time of drugs. Mucoadhesive rectal formulations have been used to treat various diseases such as hypertension and colon cancer. Ulcerative colitis (UC) is an inflammatory bowel disorder, mainly characterized by chronic inflammation of the colonic mucosa. It is commonly treated with sulfasalazine (SSZ), which is easily metabolized by intestinal flora and is biotransformed into the therapeutic 5-aminosalicylic acid (5-ASA) and a toxic by-product, sulfapyridine (SP). SSZ is mainly administered by the oral or rectal routes. The rectal route avoids unintended absorption of the drug or its degradation products in the upper gastrointestinal tract, because of the limited retention time.

In one study, a mucoadhesive hydrogel of catechol-modified chitosan (cat-CS) crosslinked by genipin was prepared to improve the efficacy of rectal SSZ administration. A UC mouse model was used to evaluate the efficacy of hydrogel with SSZ. In comparison with oral SSZ treatment, rectal SSZ/cat-CS delivery was more effective, showed equivalent histological scores, and induced a lower plasma concentration of the potentially toxic SP by-product. These results showed that SSZ/cat-CS rectal hydrogels are more effective and safer formulations for UC treatment than oral SSZ [49, 50].

5.30 Chitosan–Doxycycline Hydrogel: A Matrix Metalloproteinase Inhibitor/Sclerosing Embolizing Agent

In one study, an injectable occlusive chitosan (CH) hydrogel containing doxycycline (DOX) was prepared as a sclerosant and matrix metalloproteinase (MMP) inhibitor. Several CH-DOX hydrogel formulations were evaluated for their mechanical and sclerosing properties, injectability, DOX release rate, and MMP inhibition. An

optimized formulation was assessed for its short-term ability to occlude blood vessels in vivo. Hydrogel prepared with 0.075 M sodium bicarbonate and 0.08 M phosphate buffer as the gelling agent presented sufficient mechanical properties to immediately impede physiological flow. DOX release from this gel followed a two-stage pattern: a burst release was followed by a slow continuous release. The released DOX was biologically active and able to inhibit MMP-2 activity in human glioblastoma cells. Preliminary in vivo testing in pig renal arteries showed immediate and delayed embolization success rates of 96% and 86%, respectively. Altogether, CH-DOX hydrogels appeared to be a promising new multifunctional embolic agent for the treatment of endoleaks [51–64].

5.31 Chitosan Hydrogels Enriched with Polyphenols

A novel injectable hydrogel of chitosan, sodium beta-glycerophosphate (Na-β-GP), and alkaline phosphatase (ALP), enriched with the polyphenols phloroglucinol (PG) and gallic acid (GA), was prepared for bone regeneration and characterized physicochemically and biologically, mainly in terms of its gelation kinetics, mineralizability, antioxidant properties, antibacterial activity, cytocompatibility, and ability to support adhesion and growth of human osteoblast–like MG63 cells. Enrichment of chitosan hydrogels with PG and GA had no negative effects on gelation kinetics and mineralizability. PG and GA both enhanced the antioxidant activity of unmineralized hydrogels. Mineralization also reduced the antioxidant activity of hydrogels containing GA. Hydrogels containing GA and PG and without polyphenols reduced the colony-forming ability of *E. coli* after 1-h, 3-h, and 6-h incubation and slowed *E. coli* growth in liquid culture for 150 min. Hydrogels with GA were cytotoxic and supported cell growth more poorly than polyphenol-free hydrogels. No negative effects of PG on cell adhesion and growth were shown [65].

5.32 Improved Sustained Release of Antigen from Immunostimulatory DNA Hydrogel

A novel antigen delivery system was developed using immunostimulatory DNA hydrogel (sDNA hydrogel) containing unmethylated cytosine–phosphate–guanine (CpG) sequences, which effectively induced an antigen-specific immune response through stimulation of the innate immune system. Relatively rapid release of antigens from the sDNA hydrogel was the main limitation of its potential. For enhancement of sDNA hydrogel potency with an improved sustained release property, a biocompatible cationic polymer chitosan was selected, which electrostatically interacted with DNA to form sDNA hydrogel. In comparison with unmixed sDNA hydrogel, chitosan–sDNA hydrogel was more stable, bound more water, was able to release antigen ovalbumin (OVA) more slowly in vitro, and provided longer retention at the injection site after intradermal injection into mice. Induction of a higher

level of OVA-specific immunoglobulin G (IgG) in serum was seen with OVA-loaded chitosan–sDNA hydrogel than with OVA-loaded sDNA hydrogel with no chitosan after intradermal immunization in mice. These results indicated that the chitosan–sDNA hydrogel was an improved sustained release formulation for efficient induction of antigen-specific immune responses [66].

5.33 Sterilization-Free Chitosan Hydrogels

In one study, chitosan hydrogels were fabricated using steam sterilization, which was a simple, rapid, and solvent-free process. The resultant hydrogels were directly applied in vitro, in vivo, and in clinical studies. Drug-laden hydrogels were fabricated by this process to exhibit nearly zero-order release for up to 7 days. Also, a double-layer hydrogel system was developed for programmed drug release. In this case, the inner layer–encapsulated drug was released after degradation of the drug-free outer layer. The dimension of the outer layer was regulated for the delayed release time of the hydrogels [67].

5.34 Novel Thermosensitive Hydrogel Based on Chitosan/Hydroxypropyl Methylcellulose/Glycerol

In this work a novel thermosensitive hydrogel was prepared in physiological conditions, using chitosan together with hydroxypropyl methylcellulose and glycerol. The hydroxypropyl methylcellulose was used to facilitate the thermogelation process via a large proportion of hydrophobic interactions. In a heavy concentration of glycerol, the polymer water sheath was destroyed, which promoted formation of hydrophobic regions and lowered the phase transition temperature. The thermosensitive hydrogels showed a gelation time within 15 min at 37 °C at a near-physiological pH ranging from 6.8 to 6.9. FTIR, XRD, SEM, and rheological, mechanical, and contact angle studies were used to characterize the prepared hydrogels. The degradability, cytotoxicity, and protein release behaviors of the hydrogels were also investigated, indicating that the thermosensitive hydrogel possessed good fluidity, thermosensitivity, and biodegradability, with low cytotoxicity and controlled-release behavior, with great potential for use in biomedical applications [68].

5.35 Synthesis and Characterization of Chitosan Hydrogels

Novel chitosan hydrogels were prepared via crosslinking with dicarboxylic acids such as succinic, glutaric, and adipic acid, with the main intention being to compare the effect of the chain length on the behavior of the material. The swelling properties were studied at different pH values and temperatures, used as regulating parameters to evaluate the swelling properties of the hydrogels. The mechanical properties of

these hydrogels were evaluated by creep recovery and stress relaxation studies, and the chitosan/succinic acid hydrogels exhibited completely viscous behavior. DSC and TGA were used to quantify the thermal behavior of the hydrogels, which revealed that the materials obtained were completely amorphous. Acetaminophen (paracetamol) was used as a positive control for the release kinetics studies. Finally, it was determined that the release process was controlled by the diffusion process [69].

5.36 Zinc–Pectinate–Sterculia Gum Interpenetrating Polymer Network Beads Encapsulating Ziprasidone HCl

In one study, ziprasidone was delivered via crosslinked low-methoxyl (LM) pectinate–sterculia gum (SG) IPN intragastric beads, which were created by simultaneous ionotropic gelation with zinc acetate and covalent crosslinking with glutaraldehyde. The effects of the pectin and SG content on the DEE and cumulative drug release after 8 h (Q8) were studied to optimize the beads, using a 3^2 factorial design. The optimized beads encapsulating ziprasidone HCl (F-O) displayed DEE values of 87.98 ± 1.15% and a Q8 of 58.81 ± 1.50%, with excellent buoyancy (floating lag time <2 min, buoyancy at 8 h >63%) and an optimum mucoadhesive effect with goat gastric mucosa. The drug release behavior was maintained by Higuchi kinetics with an anomalous transport mechanism. Analytical tools such as SEM, FTIR, DSC, and P-XRD were used to characterize the Zn–pectinate–SG IPN beads [70]. Figure 10 shows response surface three-dimensional (3D) plots and contour plots illustrating the effects of the LM pectin and SG amounts on DEE and on Q8(%). Figure 11 shows SEM images of Zn–pectinate–SG IPN beads (F-O) showing a rough surface at low magnification (×75) and the presence of pores and channels at high magnification (×900). Table 4 shows the experimental plan of the 3^2 full factorial design (with coded values in parentheses), with observed response values and various physical characteristics.

5.37 Chitosan-Based Nanoparticles for Oral Drug Delivery

Cationic chitosan and anionic egg albumin with PEG 400 were used with an interpolymeric complexation technique to develop novel nanoparticles for oral delivery of alprazolam, using a heat coagulation method at pH 5.4 and 80 °C. Nine different formulations were prepared with variable concentrations of chitosan, PEG 400, and heating times. The DEE of these nanoparticles was within the range of 68.12 ± 1.27 to 99.37 ± 4.86%. FTIR, DSC, powder XRD (P-XRD), and FE-SEM analytical techniques were used to characterize the nanoparticles. The average particle diameter, polydispersity index, and zeta potential of these nanoparticles were found to be 259.60 nm, 0.501, and −9.00 mV, respectively.

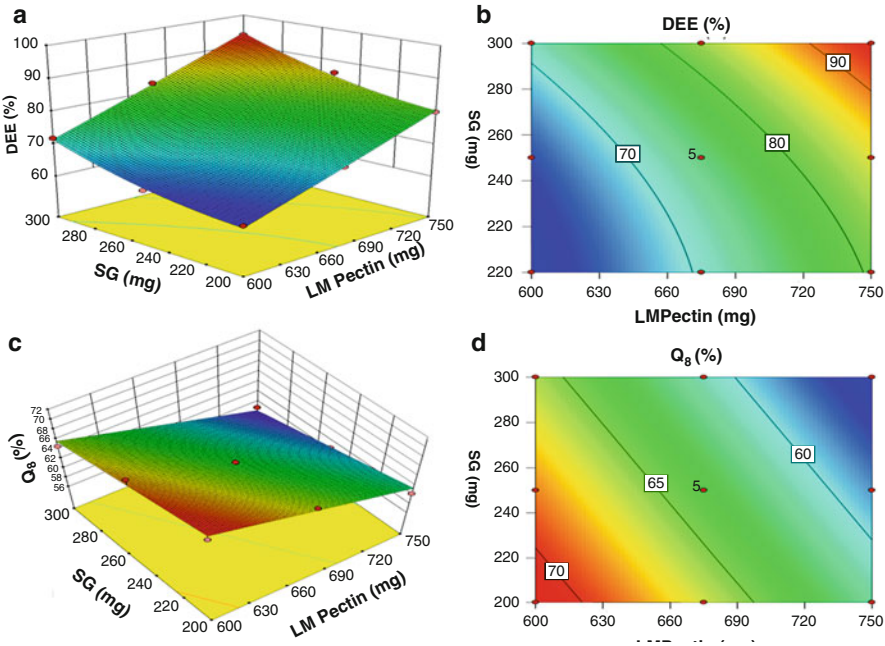


Fig. 10 Response surface three-dimensional (3D) plots (**a**) and contour plots (**b**) illustrating the effects of low-methoxyl (LM) pectin and sterculia gum (SG) amounts on the drug entrapment efficiency (DEE) percentage. Response surface 3D plots (**c**) and contour plots (**d**) demonstrating the effects of LM pectin and SG amounts on the cumulative drug release percentage after 8 h (Q8(%)). (Reproduced from Bera et al. [70], copyright © 2015, with permission from Elsevier Ltd.)

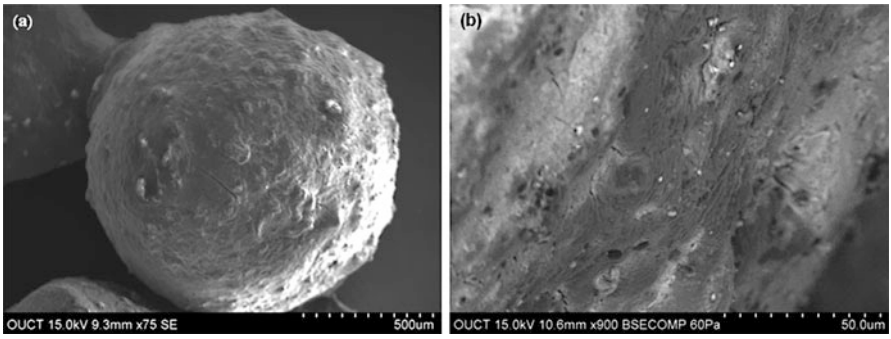


Fig. 11 Scanning electron microscopy images of Zn–pectinate–sterculia gum (SG) interpenetrating polymer network beads (F-O) showing a rough surface at low magnification (×75) (**a**) and the presence of pores and channels at high magnification (×900) (**b**). (Reproduced from Bera et al. [70], copyright © 2015, with permission from Elsevier Ltd.)

Table 4 Experimental plan of 3^2 full factorial design (with coded values in parentheses) with observed response values and various physical characteristics. (Reproduced from Bera et al. [70], copyright © 2015, with permission from Elsevier Ltd.)

Formulation code	Factors with normalized levels		Responses		Diameter (mm)[a]	Density (gm/cm^3)[a]	Floating lag time (min)[a]
	LM pectin (mg, X_1)	SG (mg, X_2)	DEE (%)[a]	Q8 (%)[a]			
F-1	750.00 (+1)	300.00 (+1)	93.62 ± 0.12	56.63 ± 1.23	2.24 ± 0.13	0.608 ± 0.18	1.33 ± 0.17
F-2	750.00 (+1)	250.00 (0)	86.37 ± 0.25	58.57 ± 0.94	1.74 ± 1.56	0.651 ± 0.12	2.66 ± 0.31
F-3	750.00 (+1)	200.00 (−1)	80.03 ± 1.23	60.32 ± 1.97	1.23 ± 0.56	0.670 ± 0.17	4.62 ± 0.24
F-4	675.00 (0)	300.00 (+1)	83.01 ± 0.89	59.64 ± 1.78	1.93 ± 0.54	0.658 ± 0.09	3.67 ± 0.33
F-5	675.00 (0)	250.00 (0)	74.47 ± 1.56	64.20 ± 1.18	1.53 ± 0.13	0.723 ± 0.05	6.35 ± 0.18
F-6	675.00 (0)	200.00 (−1)	70.45 ± 1.78	66.80 ± 3.32	1.17 ± 0.15	0.856 ± 0.02	5.65 ± 0.22
F-7	600.00 (−1)	300.00 (+1)	71.91 ± 1.37	64.72 ± 0.29	1.80 ± 0.09	0.756 ± 0.16	7.41 ± 0.46
F-8	600.00 (−1)	250.00 (0)	63.36 ± 0.47	69.67 ± 0.34	1.45 ± 0.74	0.739 ± 0.13	7.01 ± 0.50
F-9	600.00 (−1)	200.00 (−1)	61.48 ± 1.36	70.52 ± 1.85	1.12 ± 0.61	0.911 ± 0.19	8.66 ± 0.67
Experimental values							
F-O	729.50	289.09	87.98 ± 1.15	58.81 ± 1.50	2.17 ± 0.13	0.612 ± 0.14	1.43 ± 0.27
Predicted values							
% error[b]			88.79 ± 0.91	57.95 − 1.46			

DEE drug entrapment efficiency, *F* formulation code, *LM* low-methoxyl, *Q8* cumulative drug release after 8 h, *SG* sterculia gum

[a]Mean ± standard deviation; $n = 3$

[b]Error (%) = [(predicted value − actual value)/predicted value] × 100

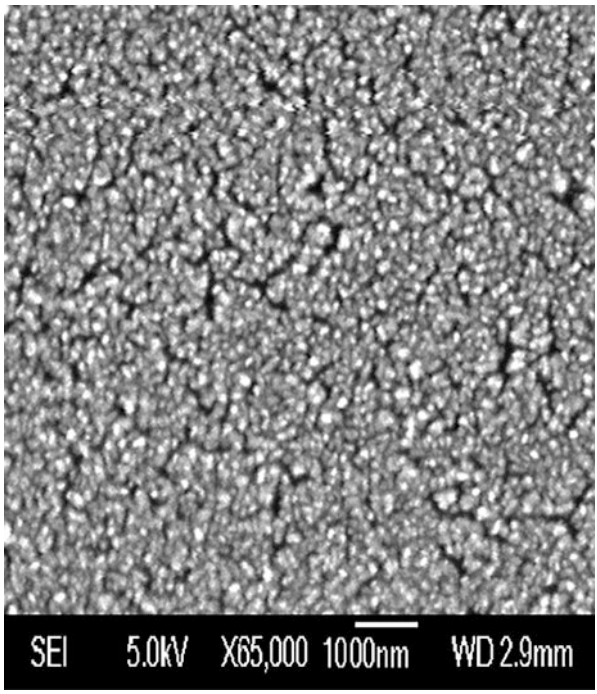


Fig. 12 Field emission scanning electron microscopy image of alprazolam-loaded chitosan–egg albumin–polyethylene glycol nanoparticles (formulation 6 (F-6)) at ×65,000 magnification. (Reproduced from Jana et al. [71], copyright © 2013, with permission from Elsevier Ltd.)

The in vitro drug release profile of alprazolam-loaded nanoparticles showed a sustained drug release pattern over a period of 24 h. These newly developed chitosan–egg albumin–PEG nanoparticles were found to be a promising vehicle for sustained release delivery of lipophilic drugs [71]. Figure 12 shows an FE-SEM image of alprazolam-loaded chitosan–egg albumin–PEG nanoparticles (formulation 6 (F-6)) at ×65,000 magnification. Table 5 shows a formulation chart for the preparation of different alprazolam-loaded nanoparticles and their DEE values.

5.38 Novel Alginate Hydrogel Core–Shell Systems Ranitidine HCl and Aceclofenac Combination Therapy

A ranitidine HCl and aceclofenac composite hydrogel system was developed on the basis of a core–shell approach. Eudragit L-100 was used to coat aceclofenac-loaded alginate microspheres and freeze–thaw crosslinked chitosan–PVA gels containing ranitidine HCl utilized as the shell-forming material. The drug encapsulation efficiency of the Eudragit L-100 coated alginate microspheres was 56.06 ± 1.12% to 68.03 ± 2.16% with average particle sizes of 551.29 ± 25.92 μm to 677.18 ± 27.05 μm. In the chitosan–PVA gels the viscosity ranged between 505.74 ± 1.04 cps and 582.41 ± 2.09 cps. FTIR, SEM, and polarized microscopy analytical techniques were used to characterize the

Table 5 Formulation chart for preparation of different alprazolam-loaded nanoparticles and their drug entrapment efficiency (DEE) values. (Reproduced from Jana et al. [71], copyright © 2013, with permission from Elsevier Ltd.)

Formulation code	Alprazolam (mg)	Egg albumin (mg)	Chitosan (mg)	PEG 400 (mL)	Heating time (min)	DEE (%) (mean ± SD; $n = 3$)
F-1	100	80	80	1.5	30	90.48 ± 4.78
F-2	100	80	80	0.5	10	86.90 ± 3.43
F-3	100	80	20	1.5	10	83.22 ± 3.06
F-4	100	80	20	0.5	30	92.62 ± 4.08
F-5	100	80	20	1.5	30	83.58 ± 3.28
F-6	100	80	80	0.5	30	99.37 ± 4.86
F-7	100	80	80	1.5	10	68.12 ± 1.27
F-8	100	80	20	0.5	10	80.14 ± 2.64
F-9	100	80	80	–	30	84.70 ± 3.42

F formulation, *PEG* polyethylene glycol, *SD* standard deviation

formulated hydrogels. The release of ranitidine HCl was comparatively higher in an acidic medium (pH 1.2) than in an alkaline medium (pH 7.4). In an alkaline medium (pH 7.4), release of aceclofenac was maintained at a slow rate and continued for up to 3.5 h. The release of ranitidine HCl in both media was assumed to follow a super case-II transport mechanism with predominance of a non-Fickian (anomalous) diffusion mechanism in the release of aceclofenac. So, these composite hydrogels were found to be highly suitable for simultaneous delivery of aceclofenac and ranitidine HCl with very minimal chances of excessive gastric acid secretion through suitable ranitidine HCl release in the gastric region [72]. Figure 13 shows SEM images of uncoated aceclofenac-loaded alginate microspheres and aceclofenac-loaded alginate microspheres coated with Eudragit L-100, and a cross-sectional view of aceclofenac-loaded alginate microspheres coated with Eudragit L-100. Table 6 lists the different formulations of aceclofenac-loaded alginate microspheres coated with Eudragit L-100, with DEE values and particle sizes.

6 Conclusion

This chapter has provided a brief overview of the field of chitosan-based hydrogels, modified or functionalized biopolymer hydrogels, and composite materials that have been used for controlled-release drug delivery. Despite their limitations, chitosan hydrogels have been extensively used in controlled drug delivery systems for various active pharmaceutical ingredients targeting site-specific activities. Natural hydrogels are in demand in biomedical science especially for developing drug formulations for targeted and slow release, tissue regeneration, and molecular engineering.

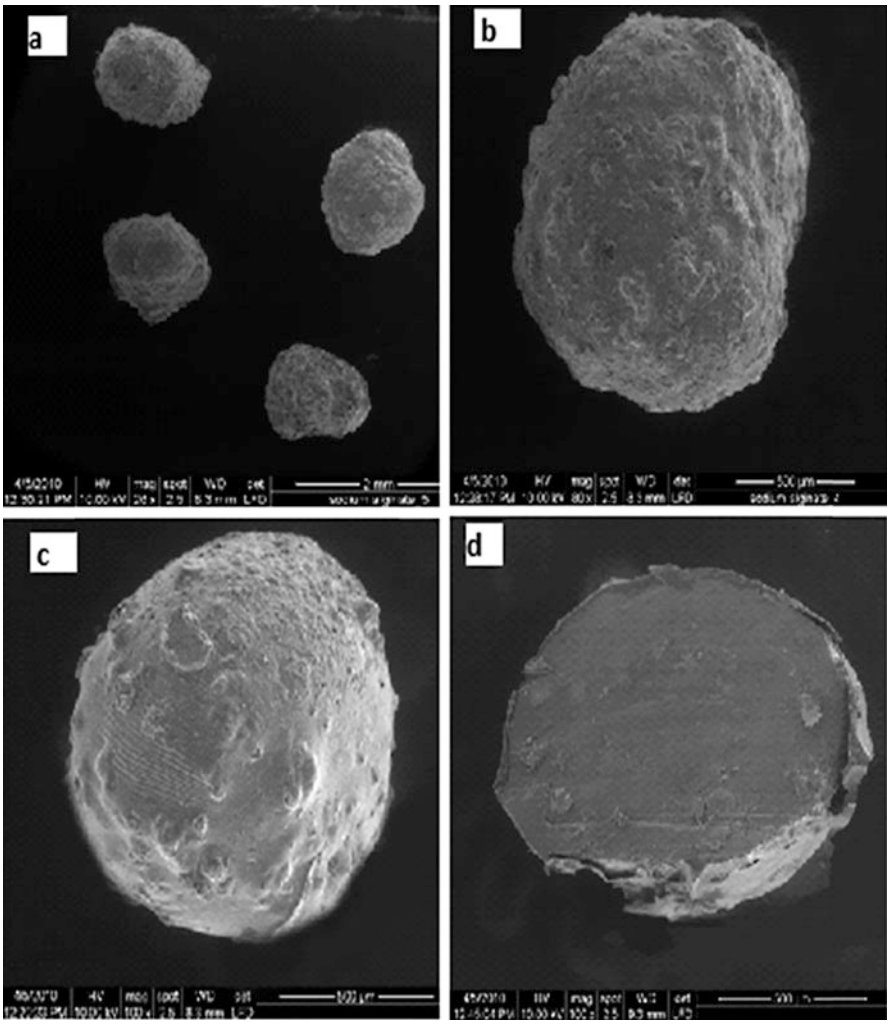


Fig. 13 Scanning electron microscopy images of uncoated aceclofenac-loaded alginate microspheres (**a** and **b**), aceclofenac-loaded alginate microspheres coated with Eudragit L-100 (**c**), and a cross-sectional view of aceclofenac-loaded alginate microspheres coated with Eudragit L-100 (**d**). (Reproduced from Jana et al. [72], copyright © 2015, with permission from Elsevier BV)

7 Future Scope

Natural polymers have been the prime choice of scientists across the world because of their biodegradable and biocompatible nature, along with their extensive applications in the fields of controlled drug delivery. Full and semi-interpenetrating polymer networks of chitosan hydrogels with silver nitrate,

Table 6 Different formulations of aceclofenac-loaded alginate microspheres coated with Eudragit L-100, with drug entrapment efficiency (DEE) values and particle sizes. (Reproduced from Jana et al. [72], copyright © 2015, with permission from Elsevier BV)

Formulation code	Sodium alginate (%)	Coating solution (mL)	Coated microspheres containing aceclofenac	
			DEE (%)[a]	Particle size (μm)[a]
F-1	3	10	64.67 ± 2.41	677.18 ± 27.05
F-2	3	5	68.03 ± 2.16	666.03 ± 21.44
F-3	2	10	57.65 ± 1.18	567.82 ± 20.12
F-4	3	10	64.92 ± 2.49	672.93 ± 21.18
F-5	3	5	65.83 ± 2.02	652.04 ± 20.42
F-6	2	5	56.06 ± 1.12	551.29 ± 25.92
F-7	2	10	58.28 ± 1.42	567.04 ± 21.55

F formulation
[a]Mean ± standard deviation, $n = 3$

thyroxine, and doxycycline as active pharmaceutical ingredients (APIs) have immune stimulatory, antibacterial, antifungal, and matrix metalloproteinase inhibitory properties, as well as many other properties. The future scope of this field will include investigation of natural polymers with their own activity profiles that can synergize the activity of APIs.

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Techno–Economic Analysis of Chitosan-Based Hydrogels Production

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Contents

Abstract

Currently, hydrogels have different applications due to its excellent water absorption capacity such as biomedical applications, absorbent materials manufacturing, chemical industries, and agroindustry industries. The hydrogels can be produced from natural, synthetic, or a combination of both sources. One of the most studied raw materials for the obtaining of hydrogels is chitosan, which is a linear

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polysaccharide that is composed of D-glucosamine and N-acetyl-D-glucosamine. Thanks to its structural and chemical properties, hydrogels based on this biopolymer are viable for biomedical applications. In this context, the aim of this chapter is to evaluate the preparation of chitosan-based hydrogels from process design point of view. An overview about chitosan-based hydrogels, main applications, description of the production process, and trends in this topic is presented. Additionally, the production of chitosan-based hydrogel using the interaction of hydrogen bonds technology is simulated in Aspen Plus generating the mass and energy balances in order to realize the technical and economic assessment of the process. The simulation shows that the even if the hydrogels from chitosan are economically feasible, there are a number of possibilities to improve the technology (to reduce the energy consumption or to improve the yields).

Keywords
Chitosan · Hydrogels · Applications · Simulation process · Techno-economic analysis

1 Introduction

Hydrogels are materials capable of absorbing large quantities of water or biological fluids due to their flexibility with a consistency similar to living tissues [1]. Hydrogels are composed of natural or synthetic materials, forming a three-dimensional (3D) network of polymer chains [2]. Therefore, some parts are solvated by water molecules and other parts are chemically or physically linked together. This structure has the interesting property that they swell but do not dissolve in aqueous medium [2]. Accordingly, these materials have diverse applications in fields such as cosmetic products, biomedical applications, and horticulture, among others [3–5]. The most common materials to manufacture hydrogels are natural polymers such as polysaccharides, which due to their biocompatibility, biodegradability, easy modification, and zero toxicity are widely studied [5, 6]. One of the polysaccharides with great applicability in the hydrogels production is chitosan because of its high availability from different fields such as medicine and biotechnology [1, 4, 7].

Chitosan is a linear polysaccharide composed of units of D-glucosamine and N-acetyl-D-glucosamine, extracted directly by the acetylation of chitin. This is considered one of the most important cationic polymers in nature because of the ability to form intracellular and extracellular hydrogen bonds [6, 8]. Chitosan-based hydrogels are physically prepared by crosslinking or chemically bonded by permanent chemical bonds. On the whole, a common way to obtain the chitosan-based hydrogels is from physical recruits [8, 9].

Despite the applications of chitosan hydrogels and different hydrogel manufacturing studies reported in the literature, no technical and economic study of the production process is presented, which is necessary to determine the large-scale

process feasibility [10–12]. Studies based on process simulation are potential tools for determining the pre-feasibility of a particular production process. Software like Aspen Plus are used to evaluate technical and economic aspects [12, 13]. This chapter addresses the subject of chitosan-based hydrogels. Theoretical concepts in terms of synthesis and application are exposed. In addition, the production process of hydrogels with the crosslinking method is analyzed in terms of economic feasibility, taking into account their large-scale simulation.

2 Chitosan

2.1 Chitosan Definition and History

The first reports on studies related to chitosan production lie in the year 1811, where it was first identified in mushrooms by French professor Henri Braconnot [14]. From this, several investigations about this polysaccharide have been made until the twenty-first century. The evolution with respect to these investigations can be observed in Table 1.

Chitosan is a linear polysaccharide composed of D-glucosamine and N-acetyl-D-glucosamine randomly attached (1–4) in varying proportions, similar to cellulose. Chitosan is present naturally in some fungi, such as those belonging to the genus *Mucor* and *Zygomycetes* [15]. However, chitosan production is based on the alkaline deacetylation of chitin (Scheme 1), which is the second most abundant polysaccharide in nature after cellulose [6, 16, 17].

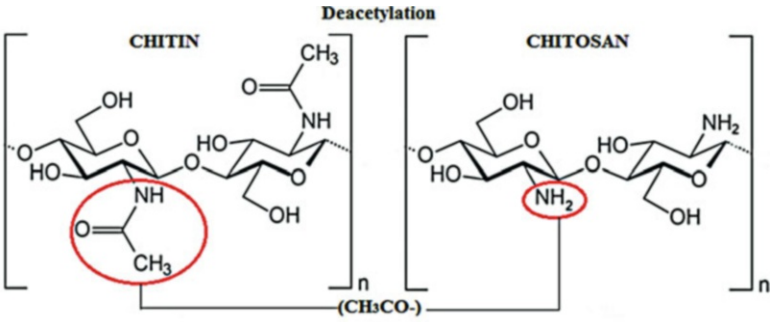
Chitin is a set of macrofibrils, being the main component of the crustacean's exoskeleton, insects, and different marine invertebrates. In structural terms, three types of chitin can be found: α-chitin, β-chitin, and γ-chitin. However, most natural chitins have an α structure, which is characterized by a compact cell, formed by alternating sheets of parallel and antiparallel chains [18].

At industrial level, about 100 billion tons of chitin are produced per year [18, 19]. This can be generated from chemical or enzymatic processes using as raw material the crustacean's residues, molluscs, insects, fungi, and marine debris. This process consists of three fundamental steps: deproteinization of the raw material, demineralization, and discoloration [18]. In general, 6.3 kg of HCl, 1.8 kg of NaOH, nitrogen, process water (0.5 t), and cooling water (0.9 t) are required to obtain 1 kg of 70% deacetylated chitosan from shrimp shells [3].

Furthermore, chitin is abundant and has advantages such as biocompatibility, biodegradability, and high mechanical resistance; however, it has solubility problems [18]. This makes chitin a limited-use polysaccharide compared to its main derivative, chitosan. The chitosan is a polysaccharide with amide and hydroxyl groups; it has the advantage to form intra- and extracellular hydrogen bonds, making it one of the main cationic polymers in nature (pKa $\approx$ 6.5) [16, 20]. Additionally, because of its biocompatibility and its nontoxic effect, it is used in medical applications, food production, and material manufacturing, among others.

Table 1 Chitosan history. (Data source: modified from Ref. [14])

Henri Braconnot	**Ojer**	**Opperman**	**Lassaigne**	**Rougeut**
Conducted research on mushrooms and extracted chitin. Hypothesis: Chitin did not dissolve in sulfuric acid	*Named "chitin," based on Greek word "khiton" meaning "envelope"*	*Chitin was extracted from insects – similar substances as chitin can also be found in the structure of insects*	*Demonstrated the presence of nitrogen in chitin*	*Discovered chitosan, observed that the substances in the chitin could be manipulated through chemical and temperature treatments for it to become soluble*
1811	1823	1832	1843	1853
Ledderhose	**Hoppe-Seyler**	**Rammelburg**	**Darmon and Rudall**	**Many researches**
Identified chitin as made of glucosamine and acetic acid	*Proposed the name of the chitosan*	*Identified more chitin sources apart from insects and fungi. Chitosan can be extracted from marine arthropods,* e.g., *crab, shrimp, and lobster*	*Structure of chitosan discovered. X-ray, the most advanced technology at the period, recorded the existence of chitin and cellulose in the cell wall*	*First book was published 140 years after the initial observation of Braconnot*
1878	1894	1930	1950	1951
Many researchers have conducted research using modified and unmodified chitosan derivative in the different fields				
1960 Till present				



Scheme 1 Chitosan production by deacetylation of chitin

2.2 Applications

The applications of chitosan are very diverse. It is presented in agriculture, medicine, industry, food, arts, etc. Due to its physicochemical and biological properties, this polysaccharide has increased its application in modern times in industrial fields such as biomedicine, papermaking, food production, agricultural applications, cosmetology, and wastewater treatment.

2.2.1 Cosmetics

Among natural antimicrobial compounds, chitosan is widely used in cosmetic applications since it can encapsulate active ingredients in different products of industrial interest. An example of this ability is the encapsulation of phenylethyl resorcinol as a skin lightener in microparticles [21]. Furthermore, because of the fungicidal properties and viscosity, this material is used in creams, shampoos, lotions, and permanent undulating lotions [3, 22].

2.2.2 Foods

Food packaging involves the use of materials that provide functional properties (antimicrobial, antioxidant) through the incorporation of active compounds into packaging materials that are usually used as films or coatings. In this sense, chitosan can be found in food in the form of biofilms, causing a protective and antibacterial effect. Such films can reduce the use of traditional synthetic packaging, which are unfriendly to the environment. Consequently, coatings applied to bread, fruit, and eggs may provide a barrier to moisture transfer and inhibit microbial growth, which increases the useful life of food [21]. Likewise, the meat is highly susceptible to lipids oxidation, leading to a rapid development of stale. However, thanks to the chitosan oxidizing effect, this can delay deterioration during storage [18, 21].

2.2.3 Wastewater Treatment

In the field of wastewater treatment, chitosan is a promising compound because of its high content of amino groups and it has an inert, biocompatible, and biodegradable nature. It can absorb organic and inorganic contaminants such as metal ions (Cu^{2+}, Hg^{2+}, Ni^{2+}, Zn^{2+}) and dye residues. In this sense, the treatment with N-benzylsulfonate derivatives demonstrated great selectivity for removal of heavy metal ions in an acid medium [3]. With respect to the absorption of dyes, chitosan has the ability to attract basic dyes and other residues (e.g., proteins), increasing the sorption rate of dye with increasing temperature [3]. Also, hydrogels have been developed for the uptake and release of dyes in wastewater, such as orange 3, disperse blue 3, and reactive black 5 [18].

2.2.4 Agriculture

Due to the antibacterial, antifungal, and antiviral properties of chitosan, it might be an excellent alternative to conventional pesticides. This allows reducing the problems caused by agriculture in natural systems, the environment pollution, and public

health concerns. As a result, this natural polymer has been successfully used as a plant protection, defense mechanism activator, and growth promoter.

Applications related to coating of cereals, nuts, fruits, and vegetables increase the firmness and favor the decrease of the microbial load, which leads to the increase of the useful life of the product [21]. Further, chitosan increases the plant production, protects plants from pathogens, and has an active effect against some insects as Lepidoptera and Homoptera (80% mortality), and the increase of chitinolytic microorganisms improves the soil microbiota and its properties [3, 21, 22].

2.2.5 Biomedicine

The biomedicine is one of the main sectors where chitosan is applied, specifically in areas related to drug administration, wound healing, artificial skin, and tissue regeneration. It offers advantages such as biocompatibility and biodegradability that are quite useful in this field. As a result, nontoxic, antimicrobial, and bioresorbable products are generated for medical applications.

Studies related to wound healing might prove that chitosan could be considered as replacement skin, which is useful for people who have suffered burns and extensive loss of skin [3, 19]. On the other hand, the intrinsic antibacterial activity, the analgesic effect, and the hemostatic activity make chitosan a suitable material for wound dressing that is useful for the treatment of external and internal bleeding lesions [18].

One of the most important applications is the controlled administration of drugs, including oral, nasal, parental, and transdermal administration [22]. Conventional dosage forms usually lead to large oscillations in serum drug concentrations, leading to uncontrolled diffusion through the body. Therefore, due to the properties of chitosan as in situ gelation, microadhesion, hydrophilic character, and improved penetration, this natural polymer is a candidate for the development of many drug delivery systems [18, 22, 23]. In addition to these properties, structural modifications of chitosan can improve the drug adsorption, transport large molecules as proteins, and have an antitumor capacity [18].

Therefore, due to the ability of hydrogels to absorb large amounts of water and drastically increase their volume, they have been widely used in this field. Many hydrogels have been designed for particular applications, chitosan/polyether hydrogels (IPN), β-chitin and poly(ethylene glycol) macromere hydrogels, poly (ethylene glycol) and β-chitosan macromer hydrogels, and chitosan/gelatin hybrid polymer hydrogels [20]. In general terms, applications of these hydrogels in the administration of drugs will be discussed later in this chapter.

2.2.6 Other Applications

Other applications of this material are found in areas such as photography, due to its abrasion resistance, optical characteristics, and film-forming ability. The contact lenses manufactured in ophthalmology with partially depolymerized chitosan have advantages because of its tensile strength, elongation, clarity, and oxygen permeability [20]. In papermaking, it is widely used to improve mechanical, barrier, and antibacterial properties. Therefore, titanium oxide (10%) nanocomposite coatings

with chitosan were effective to improve the paper characteristics in terms of gloss, opacity, air permeability, and antibacterial activity [18]. Likewise, various applications in relation to textiles, cholesterol reduction, industrial applications, and other applications are found in various studies [3, 21, 22, 24, 25].

3 Hydrogels Based on Chitosan

The use of hydrogels based on natural polysaccharides has been widely studied currently, due to its compatibility with biological means, ability of chemical interaction with tissues of the organism, and biodegradability, among others. In general, natural hydrogels can be obtained by chemical and physical methods, creating three-dimensional networks that are swelled with water. Chitosan is a polysaccharide derived from the deacetylation of chitin and has been one of the most used for the formation of physical and chemical hydrogels, films, fibers, and plastics, applied for different purposes. This polysaccharide is readily diluted in acid solutions of low concentration.

Particularly, chitosan hydrogels can absorb considerable amounts of compound fluids as drugs, in addition to large amounts of water due to the presence of the hydroxyl group (-OH) along the polymer chain. It also remains insoluble due to the existence of a three-dimensional mesh in the structure of the chitosan hydrogel. Therefore, depending on the physical or chemical methods that are applied in the production of chitosan hydrogels, problems can appear such as low mechanical resistance by alternatives that have been chosen to stabilize these hydrogels such as chemical crosslinking, reinforcement with nanostructure, and different blends of polymers [6, 26, 27].

3.1 Physical Hydrogels of Chitosan

The term "physical hydrogel" describes non-covalently crosslinked network to distinguish it from chemical hydrogels formed by covalent bonds [28]. For polysaccharide hydrogels, the term "junction zone" has often been used to describe the crosslink because each crosslink involves aggregates of ordered molecular chains like helices [29]. The bonds involved in the junction zones are generally non-covalent bonds such as hydrophobic interactions, micellar packing, hydrogen bonds, ionic bonds, crystallizing segments, and combinations of these interactions [30]. In this sense, the physical hydrogels tend to be weak because of the number of interactions along the entire polysaccharide chain. Also, they present a rather complex structure. Though it is important to take into account the conditions of the environment in which the hydrogel is introduced, it makes certain forces of attraction or repulsion predominate, causing the hydrogel to break or incorporate water into its structure [27].

Accordingly, there are currently two general methods for producing physical hydrogels of chitosan. The first method is based on the formation of rigid chitosan

hydrogels by the evaporated a solution of chitosan an acetate in presence of a mixture of water and alcohol. The second method is based on the gelling of a solution of chitosan in an atmosphere of ammonia [26].

Regarding the formation of physical hydrogels, three important conditions must be considered in the process. The first condition relates to the initial concentration of the polymer, and it has to be higher than the critical crosslinking concentration of the chain. The second condition is that hydrophilic and hydrophobic interaction must be brought to a critical equilibrium value. To achieve this critical value, the apparent charge density is reduced or the dielectric constant of the medium to which the polymer is subjected to the formation of the hydrogel is lowered. Finally, a percolating mechanism is induced that is produced by physicochemical perturbations at a bidimensional scale [31].

3.1.1 Chitosan Hydrogels in Hydroalcoholic Medium

To form the chitosan physical hydrogels in a water-alcohol medium, it is necessary to apply the abovementioned conditions. Also, it is important to take into account the initial concentration of chitosan to obtain stable physical crosslinks of the polymer chains. Contrastingly, the critical value of equilibrium among hydrophilic and hydrophobic interactions, it can be achieved by the homogenous decrease of the ionization of the chitosan polymer. The method is based on the evaporation of a solution of chitosan in a hydroalcoholic medium, method that is detailed in [32].

It is important to emphasize that during the evaporation of the chitosan solution for the formation of the hydrogel, the researchers produced a percolation gelation that represents the displacement of an interface that is deposited in the bottom of the reactor. Therefore, to obtain the chitosan solution, it was dissolved in an aqueous mixture of acetic acid, to give way to the stoichiometric protonation of the $–NH_2$ groups. The solution was mixed whit 1,2-propanediol until get final polymer concentration of 0.5% (w/v). The mixture was stirred and allowed to evaporate to a point of gelation. As for the water-alcohol medium, its function is to reduce the dielectric constant of the medium and also favors the formation of hydrophobic bonds between segments of the chitosan polymer chain. Finally, the researchers neutralized the hydrogel and washed with water the remaining acetic acid and 1,2-propanediol from the process, to obtain only the chitosan hydrogel with water [32, 33].

It is important to note that the acetyl groups gave way to the formation of hydrophobic interactions that are responsible for the formation of the chitosan hydrogel. Also, for the success of this method, it is necessary to control three important aspects [32]:

- The degree of neutralization.
- The hydrophobic character of the solvent, together with the chitosan structure.
- Molecular mobility that is dependent on the method that is used for the formation of the hydrogel.

3.1.2 Double-Layer Physical Hydrogels

According to [31], the double-layer physical hydrogels are generated in a dissolution of chitosan hydrochloride in hydroalcoholic medium forming a chitosan rigid gel layer. The water-alcohol solution is subsequently evaporated to decrease the hydroelectric constant. The acid is partially removed and a soft gel layer is formed. In this way, the charge density of the chitosan was brought to a critical point. For the second layer, the researchers added an aqueous solution of chitosan chlorate hydrate, and then the surface was partially dissolved in the presence of an acid medium to induce reprotonation of the NH_2 sites. Finally, the system was brought into contact with gaseous ammonia; in this way, the apparent charge density of the former decreased, causing hydrophobic interactions and hydrogen bonds to obtain the second layer of the chitosan hydrogel.

Ammonia was chosen mainly because it has high volatility at a temperature and ambient pressure, determining an equilibrium in the atmosphere for the gel production. Because of the above, the ammonia diffuses more easily in the acid to neutralize it and in addition, it contributes to the neutralization of the amine functions [6, 31, 33]. Figure 1 shows the steps described above for obtaining double-layer hydrogel, wherein L1 refers to layer one, formed by evaporation of the chitosan solution in a hydroalcoholic medium. On the contrary, L2 refers to the second layer that is synthesized by contacting ammonium gas with the soft chitosan gel. Lastly, the hydrogel was washed to remove the 1,2-propanediols from the first layer in addition to ammonium chloride and excess ammonia from the second layer, finally obtaining only a chitosan gel, charged with water.

3.2 Chitosan Chemical Hydrogels

Chemical hydrogels are characterized by forming a network with covalent bonds of macromolecules, attributing the capacity to swell in the water presence without

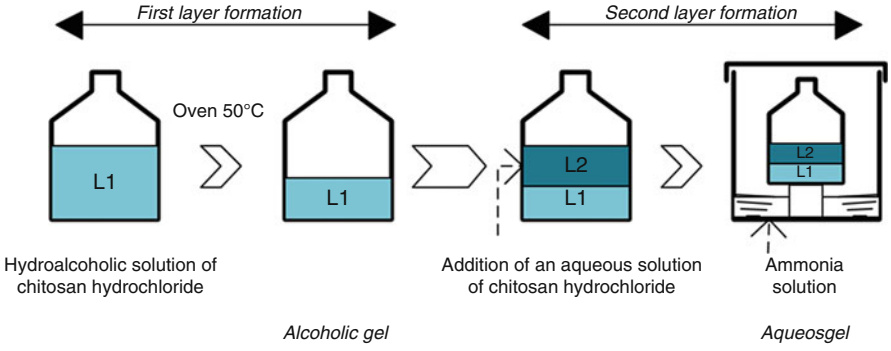


Fig. 1 Physical hydrogel formation of chitosan double layer by two different processes. One in a hydroalcoholic medium and one in an ammonia gas medium. (Data source: modified from Ref. [31])

losing the initial structural form [34]. These hydrogels are bound to different crosslinking compounds such as glutaraldehyde, formaldehyde, epoxy compound, and dialdehyde [34–36]. Covalent bonds formed with a crosslinker result in a polymer network with stable mechanical properties, useful in drug administration and the controlled release of water in crops. Apart from these, the type of crosslinker and its degree of crosslinking directly affect the swelling properties, elasticity, and molecule transport [35].

In order to obtain chemical hydrogels, the depolymerization of short chain (low-molecular-weight) monomers in contact with the crosslinking agent is necessary [37]. Besides, chemically crosslinked hydrogels can be synthesized by three types of polymerizations: chain growth polymerization, addition-condensation polymerization, and gamma-electron beam polymerization [35]. The methods for synthesizing chemical hydrogels of chitosan are based on solubilizing chitosan at a solution of formic and acetic acid prior to the interaction with the crosslinker. However, other studies report another class of chitosan solubilizers such as the adipic, glutaric, and succinic when the agent crosslinker is the carboxylic acid [38]. Therefore, depending on the application, chemical hydrogels are synthesized with a different crosslinker which provides unique characteristics to the hydrogel to apply it in a specific medium. In this way, in this chapter are described two current interest methods.

3.2.1 Crosslinker Addition in Chitosan Hydrogels

Chitosan hydrogels formed by certain chemical crosslinks have important antimicrobial properties for biomedical applications. Therefore, these have been widely studied to mitigate the growth of bacteria with resistance to pharmaceutical products [39]. However, the polymeric network bonds (covalent or ionic) depend on the class of crosslinking agent [40].

In particular, the chitosan hydrogels which are covalently crosslinked are presented in three different types according to its structure. The first type is crosslinks between the polymer networks of the same chitosan. These may involve two units of the polymer structure that belong or not to the same polymer chain (Fig. 2a). The second type is the hybrid polymers, where reactions involved for the hydrogel production are given between a chitosan chain and a polymer chain of another type (Fig. 2b). Finally, the covalent crosslinking occurs between medium or fully interpenetrating polymer networks, where unreacted semi-interpenetrating polymer networks are trapped in the hydrogel (Fig. 2c).

Covalent crosslinks may be toxic depending on reactions between the polymer chain of the chitosan and the crosslinking agent, which has led researchers to look for other alternatives such as reversible ionic crosslinks to eliminate this type of risk (Fig. 2d) [39–41]. This type of hydrogels is produced by reactions with negatively charged compounds (ions or molecules), forming a polymer network that is bound by ionic bridges [40, 42]. Hydrogels with ionic crosslinks can be applied as controlled release agents of drugs in geometric forms such as spheres, films, and sponges, among others. Accordingly, the spherical shape has been studied in the

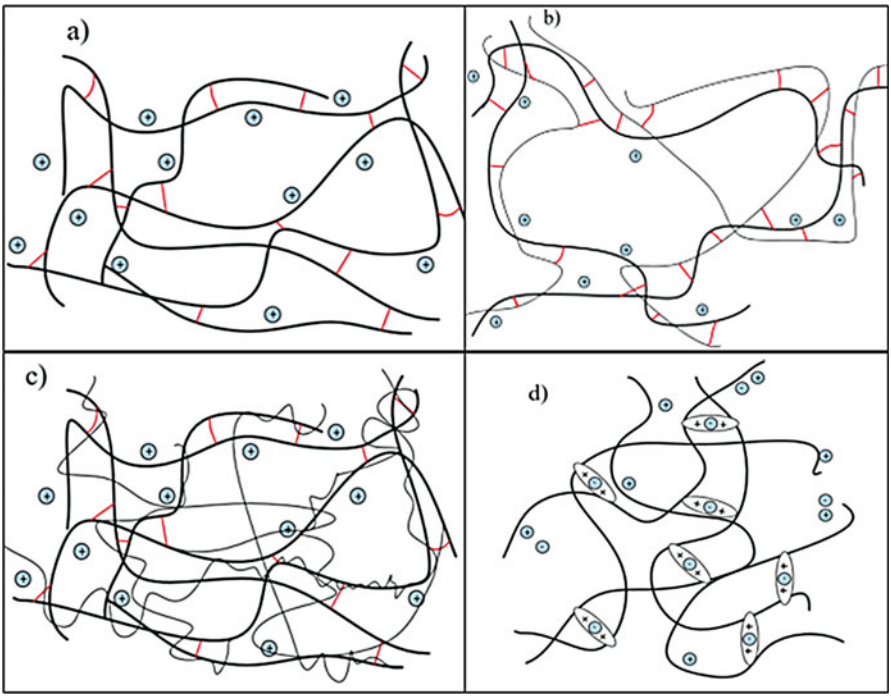


Fig. 2 Structure of chitosan hydrogels formed by (**a**) chitosan crosslinked with itself; (**b**) hybrid polymer network; (**c**) semi-interpenetrating network; (**d**) ionic crosslinking. (Data source: modified from Ref. [40])

release of 6-mercaptopurine, the films in the release of theophylline, and the sponges in the release of drugs for bone regeneration [43–45].

3.2.2 Chitosan Hydrogels by Diels-Alder Reaction

The chitosan chemical hydrogels are currently used in medicine for controlled drug administration, because the chemical synthesis of these hydrogels has a high mechanical strength for the delivery of aqueous substances in long times, preventing the network from breaking before finishing the diffusion in the medium. These hydrogels are advantageous in regard to their high adhesiveness and prolonged functioning to treat burns, chronic diseases type, and also applications in the treatment of bacteria [42, 46].

Particularly, the chitosan hydrogels crosslinked by Diels-Alder reactions are produced in three stages: in the first stage by using furan-functionalized chitosan, gelatin (Cs-Fu) is synthesized, forming the imine group between the aldehyde and the amino group of chitosan [47]. In the second stage, chitosan gelatin was synthesized with maleimide (Cs-AMI) by amide coupling [48]. In the third step, the chitosan hydrogel is formed by the reaction of the Cs-Fu and Cs-AMI derivatives.

This method is based on dissolving the separated derivatives in aqueous acetic acid solution.

The researchers determined that the proper formation of Cs-Fu and Cs-AMI gel has to be performed at a concentration of 5% w/v. Consequently, if the experiment is done at lower concentrations, the gel is not formed, and at higher concentrations, the derivatives are not solubilized. This method is important because it improves the stability of the hydrogel by causing the solubility and release of aqueous substances in biological media to be controlled. On the other hand, the method improves the hydrogel elastic properties and swelling of the net in the presence of an aqueous solution. Regarding the applications of this hydrogel, the results were successful by controlling completely *E. coli* and moderately the bacterium *S. aureus* [49].

3.3 Applications of Chitosan Hydrogels

3.3.1 Biomedical

At the present time, the hydrogels of chitosan according to the method of synthesizing physical or chemical can be applied to different science from engineering to medicine, due to its properties intrinsic properties. Today's pharmaceutical applications of chemical hydrogels have been among the most studied due to its great porosity. This property is generated by the formation of the covalent and ionic bonds of the crosslinking. Particularly in the case of these hydrogels, the chemical crosslinks of the polymer networks of chitosan are permanent. In addition, the mechanical properties of the hydrogel improve remarkably due to their stability, avoiding the collapse of the structure. Therefore, they are utilized as liberators of aqueous substances in different means. According to the above, there are two main functions of these covalent hydrogels: the first is related to the gradual release of drugs (bioactive materials) by diffusion and the second is referred to the administration in humans. In this case, the release of drugs should be widely evaluated because auxiliary molecules can be formed in the hydrogel matrix which could be toxic to humans [40, 42].

It is important to remark that diffusion of the drug into a medium depends on the crosslinking density of the hydrogel. This is important to determine the reaction parameters which control the release of a drug. For this reason, the systems with low crosslinking release a certain aqueous substance continuously. In accordance with the above, it can be concluded that the gradual increase in density is inversely proportional to the crosslinking of the chitosan hydrogel and it has the effect of decreasing the water content in the gel. Likewise, the swellability also decreases because the gel relaxation times are slower, which translated in a slower release of a particular drug and the reduction of the polymer network. Albeit, if the amount of the crosslinking agent increased, the formation of hydrogen bonds with the water molecules diminishes [40]. The biomedical applications of hydrogels crosslinked between chitosan chains are shown in Table 2.

Table 2 Reticulated chitosan hydrogels for biomedical applications. (Data source: modified from Ref. [40])

Crosslinker	Controlled release systems	Biomedical applications
Dialdehído, Glutaraldehído	Membranes for controlled delivery of riboflavin	Scaffold for hepatocyte attachment
	Transdermal delivery of oxprenolol HCl or propranolol HCl	Scaffold for the immobilization of enzymes producing dextranase or of tyrosinase for the production of L-DOPA
	Fibers for 5-fluorouracil release	Gel particles for sorption of heavy metals
	Freeze-dried microspheres for release of goserelin	Film for the fabrication of an amperometric glucose biosensor
Various, Genipin	Injectable microspheres	Biocompatible and biodegradable materials for use as implants, blood
	Gel beads for the controlled release of indomethacin	Substitutes, or wound dressing material

3.3.2 Agriculture

The high demand for agricultural production in the world has led to the optimization of this sector in terms of production associated with crop improvement. Therefore, improvements in the pest control, nutrient management, and irrigation systems meet the water needs of crops. According to the above, scientists have investigated materials that release in a controlled and continuous way, different types of nutrients as well as water to maintain moisture in crop soils. For example, materials such as polysaccharide hydrogels have been one of the most studied because there is zero toxicity and there is complete biodegradability, being viable for applications in the agricultural sector [50].

In particular, chitosan hydrogels can be effectively applied to this sector because of their hydrophilic and ecological properties. Also, the availability of this polysaccharide is high whereby the production of chitosan hydrogels for agriculture applications is tempting. Though the chemical methods are the most suitable for the hydrogel formation, the mechanical strength is greatly improved, preventing the collapse of the structure in short times. This makes the supply of nutrients and water to the crops efficient. It is also important to keep in mind that, depending on the process and type of crosslinking agent, a greater or lesser porosity will be obtained in the gel, facilitating or difficulting the incorporation of water into the hydrogel matrix [42, 51].

One of the most important chemically crosslinked hydrogels for the administration of nutrients in soils is the superabsorbent hydrogel of carboxymethyl chitosan-g-poly (acrylic acid)/attapulgite [52]. The absorption capacity of fertilizers in the matrix of this hydrogel is quite good due to its biocompatibility with the active compounds of fertilizer in an aqueous medium. The release of nutrients is administered slowly and in adequate quantities. In consequence, the loss of nutrients is minimal and improves the amount of water available in the soil. If the discharges of fertilizer and water are exaggerated, the kinetics of release of the hydrogel is

regulated by adding particular inorganic compounds. Hence, there are two methods for loading chitosan gels with nutrients [50]:

1. **Post-loading**: The gel is loaded with the active substance diffused into the network by absorption, once the gel has been formed by a chemical crosslinking method.
2. **In situ**: The gel is loaded with the active substance in the forming process. For example, when physical hydrogels of chitosan are formed, the nutrients can be loaded by absorption through washing with a water-nutrient mixture in the stage of removed acetic acid and 1,2-propanediol.

In summary, the hydrogels of chitosan for administer of nutrients and humidity to the soil are very useful because it would be eliminated the loss of fertilizers by leaching associated with factors such as porous: soils, high rainfall frequency, among others. In consequences, this type of hydrogels is effective in the conditioning of soils for crops [42, 50].

3.3.3 Foods

In the food industry, chitosan hydrogels can be found as the basis for the immobilization of enzymes. In consequence, these improve the conditions of manufacture, transport, and storage of food. Furthermore, the presence of hydrogels offers advantages such as nontoxicity with protein affinity, physiological inertia, and a broad biocompatibility. The chitosan hydrogels formed by crosslinking with genipin or aldehydes are used as substance supports, for example, in the biomaterial formation with an improvement in the mechanical resistance of the hydrogel, also as support for the absorption of dyes. Chitosan hydrogels synthesized with glutaraldehydes have been successful lately, although the crosslinks with genipin that are between 5000 and 10,000 are less cytotoxic. Though the results have been positive, biocatalysts with a good thermal equilibrium have been obtained. Besides, the hydrogels formed with genipin have been developed for applications in the lipase immobilizers because this is a highly active biocatalyst [53].

3.3.4 Wastewater

The contamination of the water resource in the world every day is made worse by human activities. In consequence, the researchers have developed different methods and materials for eliminating pollutants from wastewater. Materials like chitosan hydrogels have been investigated due to the matrix of crosslinked can absorb metallic ions from polluted waters. However, it is important to study widely methods (chemical and physical) for the formation of chitosan hydrogels with high affinity for the metal ions.

In particular, hydrogels formed from acrylamide and chitosan have important advantages for forming structural compounds with affinity for ion absorption. However when increase of pH in the solution tends it increases the absorption of the metal. In the literature is reported the absorption of ions Fe^{2+}, Ni^{2+}, Mn^{2+}, Mg^{2+}, Al^{3+}, Zn^{2+}, and Cu^{2+} in hydrogels formed from acrylamide and chitosan, with good

electronic affinity mainly for Mg^{2+}, Cu^{2+}, and Ni^{2+} ions. This type of hydrogels is used for the absorption of metal ions in wastewater generated in the automotive industry [54].

4 Techno-Economic Analysis of Hydrogels Production from Chitosan

4.1 Simulation Process

Chitosan hydrogels were formed by applying a batch process using a physical method in an atmosphere of ammonia [26]. The process is divided into four stages. In the first stage, a mixer is used to dissolve the chitosan, with an aqueous solution of acetic acid. This section is very important since the chitosan concentration determines the hydrogel properties with respect to its absorption capacity. In step 2, silver nitrate ($AgNO_3$) is added to the solution of chitosan and acetic acid. The $AgNO_3$ acts as a bridge between the amino groups of the polysaccharide. Consequently, in step 3, the resulting solution (chitosan-acetic acid-$AgNO_3$) is subjected to an ammonia atmosphere for 24 h. The ammonia atmosphere forms the hydrogel by non-covalent bonds between the silver and NH_2 of the chitosan polymer chain (Fig. 3). Finally, the solution is washed with distilled water until a neutral pH is attained.

4.2 Process Description

The production of chitosan-based hydrogels was modeled in the Aspen Plus simulation tool (Aspen Technology Inc., USA), considering a feed rate of fresh chitosan of 1 ton/day. The simulation in Aspen Plus for the process of obtaining physical hydrogels of chitosan was given in four steps (Fig. 3).

In the first step, chitosan is mixed with 2% v/v aqueous acetic acid until reaching a concentration of 2% w/w. The conditions of the mixer are given at a temperature of

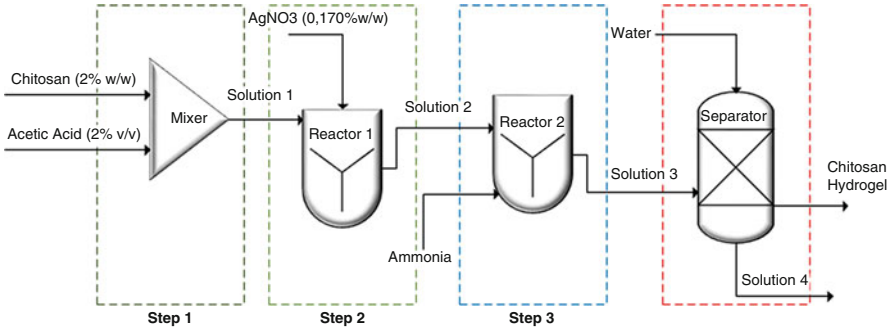


Fig. 3 Scheme of hydrogel production from chitosan

25 °C and at the pressure of 1 atmosphere. The second step is the reactor 1, in which the acetic acid and chitosan solution enters to be mixed with silver nitrate and to form the chitosan-$AgNO_3$ solution by agitation.

The reactor conditions are at a temperature of 25 °C and 1 atm. In the third step, the solution 2 (chitosan-$AgNO_3$) is introduced into reactor 2, and brought into contact with an ammonia atmosphere (analytical grade) for 24 h, forming the hydrogel. This medium regulates the pH of the acid solution, initiating the gelling. The reactor conditions are 25 °C and 1 atm. The ammonium gas on contact with solution 2 infiltrates into the matrix, which reacts with the acetic acid to form ammonium acetate, which is removed by washing with distilled water. The physically crosslinked hydrogel with Ag + forms non-covalent bonds with the $–NH_2$ groups. Finally, in step 4, the solution 3 is washed and neutralized with distilled water to obtain the fully formed chitosan hydrogel [26].

Thus, mass and energy balances were determined by calculating the activity coefficients with the NRTL activity coefficient model in the liquid phase and the Hayden-O'Connell equation of the state in the vapor phase. Finally, the simulation process allowed the calculation of the hydrogel yields per kilogram of raw material.

Table 3 shows the yields in the production of chitosan hydrogels, using silver nitrate as a crosslinking agent. The outlet molar fraction of chitosan with respect to the inlet increases because ammonia nitrate is formed by eliminating the acid side of the chitosan solution. This translates into greater crosslinks of the chitosan polymer chains between NO_{-2} and Ag^{+}.

However, the silver nitrate in the chitosan hydrogel formed in the simulation was 0.0523% by weight, which is acceptable since it is within the range (0.064–0.424% by weight) as presented in [26]. The traces of acetic acid and ammonium nitrate were washed with water as mentioned above, so they are not associated in considerable amounts in the chitosan hydrogel.

4.3 Economic Assessment

The economic assesment of hydrogel production was performed in terms of capital costs and operating costs at Latin American conditions (Colombia case), which is done in order to determine the cost of production per kilogram of product. The specific conditions were raw material costs, tax rate (33%), salaries of operators and supervisors, and return interest rate (17%), among others. The process was

Table 3 Yields in the production of chitosan hydrogels

Mass fraction	CTS-AA-$AgNO_3$	Hydrogel
Silver Nitrate ($AgNO_3$)	0.0018	0.0068
Acetic Acid (AA)	0.0195	0.0000
Water	0.9554	0.9296
Chitosan (CTS)	0.0209	0.0636
Ammonia	0.0024	0.0000

performed in the Aspen Economic Analyzer software (Aspen Technologies, Inc., USA) where operating, utilities, administrative, labor, and plant maintenance costs were calculated. Additionally, straight-line method was applied in the capital depreciation, considering a 10-year project life. Moreover, the net present value (NPV) was determined to evaluate the economic profitability of the process, which is a parameter that indicates the benefits of the plant during its useful life (in this case 10 years). The main input data used in the economic assessment are presented in Table 4.

Economic assessment was performed in terms of total production costs taking into account raw materials, utilities, operating costs, maintenance costs, and administrative costs, among others. This evaluation was based on the simulation results and Aspen economic analyzer parameters to Colombian conditions. Economic assessment results are presented in Table 5. These results show that the largest contribution to total production costs is raw materials, accounting for approximately

Table 4 Input parameters for economic assessment

Component	Price	Units
Utilities		
Electricity	0.06[a]	USD/kWh
Water process	1.252[a]	USD/m^3
High P. Steam (105 bar)	9.86[a]	USD/ton
Mid P. Steam (30 bar)	8.18[a]	USD/ton
Low P. Steam (3 bar)	1.57[a]	USD/ton
Reagents		
Chitosan	12.00[b]	USD/kg
Acetic acid	0.50[c]	USD/kg
Silver nitrate	350.00[c]	USD/kg
Ammonia	0.21[c]	USD/kg
Operator and supervisor		
Operator	2.14[a]	USD/h
Supervisor	4.29[a]	USD/h

[a]Average price in Colombian context [55]
[b]Chitosan price based on the industrial price of Ensium [56]
[c]Average prices based on Alibaba International Prices [57]

Table 5 Annualized production costs of hydrogels production

Item	Cost (USD/year)
Total raw materials cost	284000000.00
Total operating labor and maintenance cost	63560.00
Total utilities cost	25113.60
Operating charges	15360.00
Plant overhead	31780.00
Fixed and general cost	22700000.00
Depreciation expense	263352.00

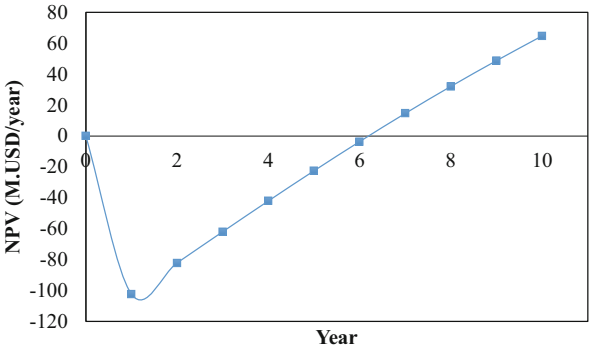


Fig. 4 NPV over life time project for hydrogels production

92% of total costs. This is not surprising because in most industrial processes the raw materials cost represents more than 50% of total costs [58].

Likewise, this result can be explained by the high costs of raw materials as chitosan and silver nitrate, which despite being in low concentrations have a great influence on the production process. Consequently, hydrogels production cost with the conditions set forth in this chapter is 3.024 USD/kg.

Nevertheless, the economic performance in terms of NPV was determined considering an estimated hydrogel market price of 3.3 USD/kg and the project life (10 years). The result is presented in Fig. 4, where it can be observed that time required to recover the initial investment and obtain positive economic margins is from the sixth year.

5 Conclusion

In this chapter, the production of chitosan hydrogels was analized with respect to the raw material, obtaining, applications, and productive process on a large scale. In summary, the main polysaccharide (chitosan) that composes these hydrogels has diverse applications due to its biocompatibility, biodegradability, and mechanical resistance. Among its main applications are the biomedicine, cosmetics, and food sector.

The importance of the chitosan hydrogels is in their biocompatibility with biological compounds and their easy biodegradability. Depending on the application, modifications are made to its properties with the manufacturing method (physical and chemical methods). For example, physical methods are preferable in biomedical applications, while chemical methods are most recommended in agriculture-related applications. Consequently, from a technical and economic point of view, the analysis of the large-scale process was developed with reference to the physical elaboration method of the hydrogel (interaction of hydrogen bonds). This determined that the hydrogel cost based on technical and economic variables is 3.024 USD/kg, which is reflected in a process feasibility for a period of 10 years.

6 Trends

Chitosan has been extensively studied to manufacture hydrogels because of its advantages with respect to other synthetic materials. Hydrogels based on this polysaccharide have wide use in applications of biocompatibility with other compounds, which represents great potential in medicine, agriculture, and industry (e.g., cosmetics, food, and wastewater treatment). Additionally, given their natural properties, availability, and low cost, important advances have been made regarding the manufacture of hydrogels with specific properties in the last decades. However, it is necessary to search for new materials and methods, which allow to reduce the environmental impacts and to reduce the final production cost on a large scale. Therefore, in order to achieve this objective, it is necessary to incorporate technical and economic studies in terms of simulation, which can save time, predict failed investments, and establish the processes pre-feasibility.

On the other hand, chitosan hydrogels applied in biomedicine will gain strength in the following years, due to the great reception regarding drug release, wound healing, and use as absorbing material, among others. Similarly, hydrogels in agriculture can extend their use with research in terms of growth assessment, plant productivity, and cost reduction. In general terms, new hydrogels incorporating chitosan into their structure will be developed due to their physicochemical characteristics and various action fields.

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Silk-Based Hydrogels for Biomedical Applications

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Abstract

Among the naturally occurring fibers, silk occupies a special position due to its properties. Silk fibroins, the unique proteins of silkworm fibers, are high-molecular-weight block copolymers consisting of a heavy (~370 kDa) and a light (~26 kDa) chain with varying amphiphilicity linked by a single disulphide bond. *Bombyx mori* silk is the most characterized silkworm silk. Researchers have investigated fibroin as one of the promising resources of biotechnology and biomedical materials due to its other unique properties including excellent biocompatibility, favorable oxygen permeability, and outstanding biodegradability, and the degradation product can be readily absorbed by the body with minimal inflammatory reaction. Silk hydrogels have been thoroughly studied for potential biotechnological applications due to their mechanical properties, biocompatibility, controllable degradation rates, and self-assembly into β-sheet networks. Hydrogels made from silk proteins have shown a potential in overcoming limitations of hydrogels prepared from conventional polymers. This chapter offers overview of the recent developments in silk protein-based hydrogels, both of fibroin and sericin proteins. It describes the approaches for obtaining silk hydrogels and ideas to improve the existing properties or to incorporate new features in the hydrogels by making composites. Characterization tools and modern bioapplications of the silk hydrogels for tissue engineering and controlled release are also reviewed. A special focus is given to silk fibroin composite hydrogels for bone tissue engineering applications.

Keywords

Silk fibroin · Graphene oxide · Composite hydrogels · Bone tissue engineering · Biocompatibility

1 Introduction

Silks are defined as protein polymers spun into fibers by *Lepidoptera* larvae such as silkworms, spiders, mites, and flies. The most studied silks in the literature are those from domesticated silkworm *Bombyx mori* and from spiders *Nephila clavipes* and *Araneus diadematus*. Silk in its natural form is composed of a filament core protein, silk fibroin, and a glue-like coating consisting of a family of sericin proteins. They provide an excellent combination of mechanical properties such as lightweight (1.3 g/cm^3), high strength (up to 4.8 GPa as the strongest fiber known in nature), and remarkable toughness and elasticity (going to 35%). In addition to the remarkable mechanical properties, silks are thermally stable up to 200 °C, allowing processing over a wide range of temperatures.

B. mori silk fibroin has been used in textiles production for centuries and for sutures in biomedical applications for decades. Also, due to its processing versatility, biocompatibility, good mechanical properties, controlled degradability, microbial

resistance, and good oxygen permeability, silk became an attractive biomaterial for biomedical applications.

Due to its high processing versatility, silk fibroin can be used as biomaterial in various forms, such as films, foams, fibers, gels, membranes, powders, sponges, and scaffolds [1, 2]. In regenerated form, silk fibroin has been used in drug delivery systems, wound protection, burn-wound dressing, ophthalmic applications, enzyme immobilization matrices, vascular grafts, nerve grafts, structural implants, and ligament tissue engineering (anterior cruciate ligament for knee joints) [1–4]. Also, silk fibroin has been blended with alginate, collagen, cellulose, chitosan, gelatin, hyaluronic acid, PVA, PEG, polyurethane, keratin, and CNTs as tissue engineering scaffolds with different biomedical applications.

Hydrogels are cross-linked, three-dimensional hydrophilic networks that swell but do not dissolve when brought into contact with water. Due to their unique properties, and desirable physical characteristics, hydrogels have been used for many applications in regenerative medicine.

Hydrogel-based silks have been thoroughly studied for potential biomedical applications due to their mechanical properties, biocompatibility, controllable degradation rates, and self-assembly into β-sheet networks.

2 Silk Fibroin

2.1 Structure and Properties of Silks

Silk, called the *Queen of fibers*, is a natural protein fiber produced by some *Lepidoptera* larvae such as silkworm, spiders, scorpions, files, and mites. The most studied silk is the domesticated silkworm, *Bombyx mori* (*Lepidoptera: Bombycidae family*).

Bombyx mori silk is a natural macromolecular protein composed of two major proteins, fibroin and sericin, which account for ~75% and ~25% of the cocoon, and also consists of fat and wax (1.5%) and mineral salts (0.5%). These proteins consist of the same 18 amino acids such as glycine, alanine, serine, and tyrosine (Table 1).

Silk sericin (10–300 kDa) is a glue-like hydrophilic globular protein that surrounds the fibroin fibers to cement them together. Sericin also provides oxidation and UV resistance and antibacterial and moisture properties and has the ability to absorb and remove water. After the degumming process, the water-soluble sericin is removed resulting a structure consisting of fibroin remains.

Silk fibroin consists of a heavy (~350 kDa) and a light (~25 kDa) chain, which are present in a 1:1 ratio, linked by a disulphide bond [5]. The silk fibroin also contains a glycoprotein, named P25, with a molecular mass of about 30 kDa [6]. The hydrophobic domains of H chains contain Gly-X (X being Ala, Ser, Thr, and Val) repeats and can form antiparallel β-sheets. The L-chain is hydrophilic in nature and relatively elastic. P25 protein is believed to play a significant role in maintaining the integrity of the complex [7].

Table 1 Amino acids composition of fibroin

Amino acids	Composition, mol%		
	Total	Heavy areas	Light areas
Glycine	42.9	49.4	10.0
Alanine	30.0	29.8	16.9
Serine	12.2	29.8	7.9
Tyrosine	4.8	4.6	3.4
Valine	2.5	2.0	7.4
Aspartic acid	1.9	0.65	15.4
Glutamic acid	1.4	0.70	8.4
Threonine	0.92	0.45	2.8
Phenylalanine	0.67	0.39	2.7
Methionine	0.37	–	0.37
Isoleucine	0.64	0.14	7.3
Leucine	0.55	0.09	7.2
Proline	0.45	0.31	3.0
Arginine	0.51	0.18	3.8
Histidine	0.19	0.09	1.6
Lysine	0.38	0.06	1.5

Therefore, silk fibroin is considered as a block copolymer composed of crystalline (hydrophobic chains) and amorphous states (hydrophilic chains). The fibroin structure contains repeating basic unit of Gly-Ser-Gly-Ala-Gly-Ala amino acid sequence. The crystalline nature of silk fibers is due to the high content of repetitive Gly-Ala-Gly-Ala-Gly-Ser sequence, and the amorphous domain is represented by amino acid sequence Thr-Gly-Ser-Ser-Gly-Phe-Gly-Pro-Tyr-Val-Ala-Asp-Gly-Gly-Tyr-Ser-Arg-Arg-Glu-Gly-Tyr-Glu-Tyr-Ala-Trp-Ser-Ser-Lys-Ser-Asp-Phe-Glu-Thr. The highly repetitive sections are characterized by the presence of glycine (45%), alanine (30%), and serine (12%), accounting for approximately 85 mol% of the total amino acids, in a rough 3:2:1 ratio, and the amino acid sequences are expressed as $[Gly\text{-}Ala\text{-}Gly\text{-}Ala\text{-}Gly\text{-}Ser]_n$ (Table 1).

Also, it is reported that silk fibroin has many hydroxyl residues based on its amino acid composition, Ser (10.6 mol%), Tyr (5.0 mol%), and Thr (0.9 mol%), by comparison with the carboxyl and amino group content which was low (3.9 mol%). The macromolecular polypeptide chain of silk fibroin has a zigzag shape, like β-keratin.

Two secondary structures can be distinguished in crystalline areas for *Bombyx mori* silk fibroin: silk I (α-helix) and silk II (β-sheet) [8]. The silk I structure is formed by intra-molecular hydrogen bonds, is water soluble, and upon exposure to organic solvents converts to silk II structure. The silk II structure is water insoluble and water soluble in various solvents [8].

In the crystalline areas of silk fibroin, the side-chain protein marked the R-group (H-glycine, CH_3-alanine and CH_2-OH-serine) is almost fully extended in β-sheet structure, allowing the formation of hydrogen bonds.

Table 2 Mechanical properties of biomaterials

Material	Ultimate tensile strength (UTS) (MPa)	Modulus of elasticity (GPa)	Elongation at break (%)
***Bombyx mori* silk sericin**	500	5–12	19
***Bombyx mori* silk fibroin**	610–690	15–17	4–16
***Bombyx mori* silk**	740	10	20
Spider silk	875–972	11–13	17–18
Collagen	0.9–7.4	0.0018–0.046	24–68
Tendon	150	1.5	12
Bone	160	20	3
Kevlar	3600	130	2.7
Synthetic rubber	50	0.001	850

The β-sheet interacts with each other only through hydrogen bonds (inter-chain and intra-chain) and van der Waals interactions, generating a flexible structure [8].

The remarkable properties of natural silk could compete with the most advanced synthetic polymers yet, unlike these, are obtained in less harsh conditions, from renewable raw materials, and are biodegradable. Silk fibers are long, thin, light, and soft.

The outstanding mechanical properties of silk fibroin characterized by high strength combined with high extensibility, and good compressibility, are due to the extensive hydrogen bonding, hydrophobic nature, and the crystalline domain orientations. Some mechanical properties of silk fiber and its components and some other biomaterials are presented in Table 2 [8].

Due to the lack of covalent linkages in the polymer system, the thermal stability of silk fibres is excellent up to 110 °C, starting with 200 °C, the chemical reactions involve the degradation of amino acid side groups with the formation of gases (CO, CO_2, NH_3).

Silk fibers have hygroscopic nature. Under normal conditions (20 °C, 65% RH), silks absorb approximately 11 wt.% of its weight in water. Water absorption causes swelling of fiber to a value of 1.6% in longitudinal direction and 18.6% in transverse direction. The specific gravity of raw silk ranges between 1.33 and 1.40 g/cm^3.

The dry silk fibroin has a glass transition at 178 °C (Tg = 451.15 K) but strongly decreases in the presence of water.

The chemical reactivity of silk fibers is high due to the amino acid side groups. This property is used for chemical modification and grafting of some monomers on the chain protein, to modify its properties.

Silk shows an amphoteric character, containing both cationic and anionic groups, which interacts according to pH. It forms salts in reaction with mineral acids or, if acids are weak, they can attach to the protein through hydrogen bonds. In an acid environment, peptide bonds are hydrolyzed.

Natural silk fibers dissolve only in a limited number of solvents due to its crystalline nature and to the intra- and intermolecular hydrogen bonds. Silk fibroin dissolves in aqueous- organic solution of salts NaSCN (sodium thiocyanate), LiSCN (lithium thiocyanate), and 9.0–9.5 M LiBr (lithium bromide); mixtures of aqueous calcium chloride and ethanol ($CaCl_2$-Et-OH-H_2O), calcium nitrate in methanol ($Ca(NO_3)_2$-Me-OH), or aqueous lithium bromide and ethanol (LiBr-EtOH-H_2O); hexafluoroisopropanol (HFIP); hexafluoroacetone; and formic acid.

2.2 Silk Fibroin Hydrogels

Silk materials can be fabricated into versatile formats, specifically aqueous-based platforms, such as hydrogels, as their properties lend utility for a diversity of medical applications.

Hydrogels are cross-linked, three-dimensional hydrophilic networks that swell but not dissolve when brought into contact with water. Due to their unique properties, and desirable physical characteristics, hydrogels have been used for many applications in regenerative medicine.

Hydrogel-based silks have been thoroughly studied for potential biomedical applications due to their mechanical properties, biocompatibility, controllable degradation rates, and self-assembly into β-sheet networks [9–11]. Silk fibroin hydrogels are also prepared by sol-gel transition in the presence of acid, ions, or other additives [12]. The gelation reaction depends on temperature, silk fibroin concentration and pH, and the concentration of additives such as Ca^{2+}, glycerol, and poly(ethylene oxide).

The major disadvantages of the silk fibroin hydrogels are their poor mechanical properties and swelling behavior, which are very important parameters in biomedical applications.

To further improve the properties of hydrogels, silk fibroin has been blended with various other polymers which include synthetic molecules such as polyvinyl alcohol, polyacrylamide, and multiwalled carbon nanotubes (MWCNTs) as well as natural macromolecules like gelatin, chitosan, and collagen [13–16].

3 Silk Fibroin Scaffolds for Tissue Engineering Applications

Silk has several major advantages over other protein-based biomaterials, which are derived from tissues of allogeneic or xenogeneic origins. Such advantages are the low risk of infection and reduced processing costs. Additionally, silk is an established textile fiber where purification is routinely carried out using a simple alkali or enzyme-based degumming procedure, which yields the starting material for sericin-free silk-based biomaterials. Silk fibroin, obtained from silkworms, demonstrates great biocompatibility along with outstanding mechanical properties [17] and proteolytic degradation [18].

In tissue engineering, silk fibroin has been extensively used for multiple types of scaffolds [19]. Various modifications of silk scaffolds have been fabricated with a wide range of chemical, structural, and biomechanical modifications [20]. Silk sponges have been used for cartilage [21, 22] and fat [23, 24], silk tubes for blood vessels [25], and silk fibers for ligaments [26]. Porous sponge scaffolds are suitable for bone tissue formation as they enhance cell attachment, proliferation, and migration. In addition, the high porosity (92–98%) facilitates nutrient and waste transport into and out of the scaffolds [27].

Silk fibroin can be combined or cross-linked with other polymers such as proteins, polysaccharides, and other synthetic polymers in order to improve its properties. The final composites usually will possess the advantages of both materials. Silk fibroin-based scaffolds can be divided into three major categories, proteins/silk fibroin scaffolds, polysaccharide/silk fibroin scaffolds, and synthetic polymer/silk fibroin scaffolds, with applications in a wide range of tissue regeneration such as neural (hyaluronic acid/SF scaffolds [28]), vascular (SF films [29], collagen/SF scaffolds [30], collagen/heparin/SF scaffolds [31]), and hepatic (poly (lactic acid) (PLA)/SF scaffolds [32]).

3.1 Proteins/Silk Fibroin Scaffolds

Proteins/silk fibroin scaffolds contain proteins that sustain cell adhesion and viability, promote cell proliferation and metabolism, and/or induce stem cells differentiation. Collagen/silk fibroin scaffolds [33] and keratin/silk fibroin scaffolds [34] are two common proteins/SF scaffolds widely used in the development of various tissue engineering strategies.

3.2 Polysaccharide/Silk Fibroin Scaffolds

Natural polysaccharides significantly improve the surface property of silk fibroin scaffolds by creating a proper roughness and also offer nutritive substrate that promotes cell growth. Chitosan/SF scaffolds [35] and hyaluronic acid/SF scaffolds [36] are commonly used polysaccharide/SF scaffolds.

3.3 Synthetic Polymers/Silk Fibroin Scaffolds

Compared with the natural polymers mentioned above, synthetic polymers have some considerable advantages like well-known structures and tunable properties. Various synthetic polymer scaffolds have been already used in tissue engineering: nylon, polyethylene (PE), ultra-high molecular weight polyethylene (UHMWPE), poly(methyl methacrylate) (PMMA), polylactic acid (PLA), and even more [37].

We have developed a composite silk fibroin and polyacrylamide scaffold containing graphene oxide nanoparticles for future potential tissue engineering applications. We have previously demonstrated that the silk fibroin and polyacrylamide scaffolds with various compositions display good mineralization potential and high biocompatibility [38].

4 Biomimetic Graphene Oxide Decorated Silk Fibroin/Polyacrylamide Composite Hydrogels for Bone Regeneration

4.1 General Considerations

Current use of reconstruction approaches in orthopedics resulted in a blossom, not only in the development of surgical procedures but also in the field of bone implants. Traditional synthetic implants are usually made of metals, polymers, ceramics, or even composite biomaterials. These materials often poorly integrate at the implantation site, thereby resulting in unsuccessful surgical outcomes due to poor corrosion, mechanical mismatch, unamiable surface environment, etc. [39].

Metallic biomaterials have traditionally been used, although their mechanical properties are different from that of bones and that they remain in the body almost permanently. Both synthetic and natural polymers have been tested, though each has its own limitations. Biomimetic materials, such as type I collagen, b-tricalcium phosphate (b-TCP), and hydroxyapatite (HAP), have attracted more attention in the last years, as a new alternate material. However, ceramic materials cannot provide a structurally complex device because of their brittle nature and low flexibility [40].

Proteins, as natural components of the tissues, are a rational choice for tissue engineering applications. Structural proteins such as collagen, elastin, elastin-like-peptides, albumin, and fibrin are already used as sutures, tissue scaffolds, and drug delivery agents [41]. Despite all the previous efforts and achievements, new scaffolds are to be designed in order to better fulfill the bone tissue applications requirements.

The ideal scaffolds should mimic the natural extracellular matrix (ECM) that supports cell attachment, proliferation, and differentiation. Consequently, scaffolds should display an appropriate biochemistry and nano-/micro-scale surface topographies, in order to provide binding sites that actively regulate and control host cell behavior in their interaction with the material. Nevertheless, the mechanical properties of the scaffolds are of important concern. Mechanical features can significantly influence the osteointegration between implants and surrounding tissues, as well as the cell behavior [39].

Since bones exhibit superelastic biomechanical properties, the ideal scaffolds should mimic its strength, stiffness, and mechanical behavior, so as to avoid bone

resorption and consequent implant failure. Additionally, an ideal scaffold should be non-toxic, non-immunogenic, and biocompatible, and it should be easily functionalized with bioactive proteins and/or chemicals [42]. Another key factor is the biodegradability of the material: the degradation rate of tissue engineering scaffolds should mirror the rate of new tissue formation [42]. Additionally, the resulting products should be non-toxic and easily metabolized and cleared from the body.

One major challenge of bone regeneration is to establish a three-dimensional (3-D) functional system, further called bioconstruct or biohybrid, that includes cells and biomaterials, and in which cells acquire nutrition, exchange gas, and excrete metabolites. This serves as a physical foundation for the development of new tissues with specific functions. Therefore, one of the prerequisites of practical tissue engineering technology is to obtain 3-D matrices with good biocompatibility [42].

Due to the unique chemical and mechanical properties and biocompatibility of silk fibroin, porous silk scaffolds for tissue engineering applications have attracted a great interest. Additionally, graphene nano-sheets have been proposed as excellent nano-filler for the preparation of the biopolymer composite materials. Graphene is a one-atom-thick sheet of C atoms, arranged in a 2-D honeycomb structure. The strong C–C bonding in the plane, the aromatic structure, the presence of free p electrons, and reactive sites for surface reactions make graphene a unique material with excellent properties. Graphene has attracted tremendous attention because of its non-toxic character, excellent mechanical properties, and high electrical and thermal conductivity [43]. Due to its particular properties, it has also been used as a biomaterial for various biomedical applications such as biosensors, biomedicine, bio-imaging, drug delivery, and biodetection [44].

Graphene–polymer/biopolymer composites showed a significant increase of elastic modulus, tensile strength, thermal stability, and electrical conductivity even at low loading of graphene filler which compensate with the fact that they are non-biodegradable [45]. Graphene oxide (GO) is an oxidized derivative of graphene [46] which contains many reactive oxygen functional groups (epoxide, carboxyl, and hydroxyl groups) which facilitate the dispersion in water and enable the interactions with proteins through covalent, electrostatic, and hydrogen bonding [47].

Based on these considerations, a combination of silk fibroin and GO may have a beneficial effect on the properties of the composites, in particular to improve the mechanical response of silk fibroin (SF) without decreasing its excellent biocompatibility. Due to the lack of knowledge with respect to the biological behavior associated with SF/GO materials on mouse osteoblastic cells, we developed a study to determine the potential use of SF/GO-based composites in the field of bone regeneration. The incorporation of GO nano-sheets into a SF-based biomaterial was intended to extend its biomedical potential use toward bone regeneration by modifying its morphological and mechanical properties.

4.2 Materials and Methods

4.2.1 Materials

Silk cocoons from *Bombyx mori* silkworms were kindly provided by Commercial Society SERICAROM SA (Bucharest, Romania). Lithium bromide (LiBr), sodium bicarbonate, and sodium dodecyl sulfate (SDS) were purchased from Sigma Aldrich and Alfa Aesar GmbH & Co KG, Germany. Dialysis tubing cellulose membrane, acrylamide (AA), *N*,*N*′-methylenebisacrylamide (MBA), triethanol amine (TEA), and potassium persulfate (KPS) were supplied by Sigma Aldrich. Graphene oxide was obtained according to Hummers [48] protocol and was supplied by National Institute for Research and Development in Microtechnologies (Romania).

Mouse MC3T3-E1 preosteoblasts (ATCC® CRL-2593™) were employed for the in vitro biocompatibility evaluation of the new composite biomaterials designed for bone tissue engineering applications. MC3T3-E1 adherent cells originate from newborn mouse (*Mus musculus*, strain C57BL/6) *calvaria* and display a fibroblast-*like* morphology. This cell line is recommended as a good model for studying in vitro osteoblast differentiation. MC3T3-E1 cells were cultivated in Dulbecco's Modified Eagle's Medium low glucose (DMEM lg) (Sigma-Aldrich, code D2902), supplemented with 3.5 g glucose, 1.5 g $NaHCO_3$, 1% antibiotic-antimycotic (ABAM) (Sigma-Aldrich, code A5955), and 10% fetal bovine serum (FBS) (Gibco, code 10106-151). All the cell culture reagents were purchased from Sigma-Aldrich, Co. (Steinheim, Germany), while the fluorescent labeling reagents were supplied by Invitrogen, Life Technologies (Foster City, CA).

4.2.2 Obtaining of Silk Fibroin/Graphene Oxide Composite Hydrogels

The silk fibroin (SF) solution was obtained after separation of silk fibroin from silkworm cocoons by the degumming process. Briefly, *Bombyx mori* silkworm cocoons were cut in small pieces and boiled in an aqueous solution of $NaHCO_3$ and sodium dodecyl sulfate (0.5% (w/v)). This process was repeated three times to obtain the pure silk fibroin fiber. The degummed fibers were dried at 45 °C for 24 h under atmospheric pressure. In order to obtain the silk fibroin solution, dried fibroin fibers were dissolved in 9.3 M LiBr aqueous solution as reported in other papers, at 60 °C for 8 h [38, 49, 50]. This solution was dialyzed in distilled water using a dialysis tubing cellulose membrane (molecular weight cutoff, MWCO, 12.4 kDa) for 4 days (frequent water changes). The final concentration of the silk fibroin aqueous solution was 3 wt.%, which was determined by weighing the remaining solid after drying.

The SF/GO hydrogels were obtained by a radical polymerization of acrylamide (AA) cross-linked with methylenebisacrylamide (MBA) in SF solution containing dispersed GO. A 15% (w/v) AA solution was mixed with 6% (w/w) *N*,*N*′-MBA and with various ratios of silk fibroin solution. The 0.1% (w/v) GO dispersion was added, and the blended solution was subjected to ultrasonication for 60 min in order to obtain a better dispersion of GO. After the addition of the redox initiating system, the solution was injected in the polymerization mold. The mold is composed of a rubber cavity between two glass plates sealed together to avoid liquid leakage.

The reaction proceeded for 4 days at 40 °C. The obtained composite hydrogels were purified by repeated extractions in distilled water for 48 h, in order to remove the unreacted AA monomer and cross-linking agent. Samples were cut into circles of 2 cm and were dried at room temperature.

The resulting 3D SF/polyacrylamide (PAA)/GO composite hydrogels were further referred as P1_SF:PAA/GO = 10:90/0.1; P2_SF:PAA/GO = 20:80/0.1; P3_SF:PAA/GO = 30:70/0.1; P4_SF:PAA/GO = 40:60/0.1; and P5_SF:PAA/GO = 50:50/0.1.

4.2.3 Spectroscopic Characterization of the Composites by FTIR-ATR and RAMAN Analyses

Fourier transform infrared (FT-IR) patterns were recorded on a Bruker Vertex 70 spectrometer in 4000–600 cm^{-1} region, equipped with attenuated transmission reflectance (ATR) accessory, using a resolution of 4 cm^{-1} and an accumulation of 32 spectra. Raman spectra of graphene oxide, silk fibroin-polyacrylamide hydrogel, and composite hydrogels were recorded on a DXR Raman Microscope (Thermo Scientific) by 633 nm laser line and a number of 10 scans. The 10× objective was used to focus the Raman microscope.

4.2.4 Swelling Behavior of the Composite Hydrogels

The swelling behavior of SF:PAA/GO hydrogels with different compositions was determined by soaking each hydrogel in distilled water at 37 °C temperature. Before each measurement of the swollen hydrogels, the excess water from the hydrogel surface was removed using filter paper. For this analysis, three samples for each composition were used. The formula used to determine the swelling degree is described below:

$$\mathrm{SD}\% = \frac{Wt - W0^{*}}{W0}\,100$$

where:

SD% – swelling degree
W_t – the weight of the wet hydrogel
W_0 – the weight of dried sample

4.2.5 Biomineralization Assessment of the Silk-Graphene Oxide Materials SEM Investigation

Biomineralization behavior of SF:PAA/GO hydrogels was assessed through Kokubo T. assay [51]. Briefly, three samples of each composition were lyophilized and then incubated for 14 days in containers with 45 mL of simulated body fluid (SBF 1×) at pH 7.45, which was adjusted with tris(hydroxy-methyl)aminomethane (Tris) and HCl. The ion composition of SBF 1× was as follows: Na^{+} 140 mM, Ca^{2+} 2.5 mM, Mg^{2+} 1.5 mM, HCO_3^{-} 4.2 mM, Cl^{-} 147.8 mM, HPO_4^{2-} 1 mM, SO_4^{2-} 0.5 mM, and K^{+} 5 mM [52]. The incubation medium was changed every 48 h.

The second biomineralization method used is known as an alternate soaking process and consists of two important steps: Step 1, the incubation of the sample in a $CaCl_2$ solution (200 mM) at 37 °C for 2 days, and Step 2, the immersion of the sample in a Na_2HPO_4 solution (120 mM) for another 2 days [53].

The presence of apatite minerals on the surface of biomineralized composite hydrogels was investigated through SEM analysis after gold coating using a Quanta Inspect F SEM device equipped with a field emission gun (FEG) with 1.2 nm resolution and with an X-ray energy dispersive spectrometer (EDS).

4.2.6 Achievement of the 3D Cell/Scaffold Bioconstruct

SF:PAA/GO dry porous scaffolds were exposed to UV light for 12 h on each side for sterilization and swollen at 4 °C for 24 h in PBS (phosphate buffered saline) buffer supplemented with 1% cell culture antibiotic-antimycotic solution (ABAM). Before use, they were cut under sterile conditions in small discs with the final area of 0.2 cm^2, to fit in the wells of a standard 96-well plate.

MC3T3-E1 preosteoblasts in the 12th passage were seeded on the surface of the materials with an initial cell density of 10^6 cells/sample. In this view, a 150 μl drop containing 10^6 cells was placed on top of each sample and allowed 30 min to diffuse through the porous scaffold in order for the cells to adhere to the inner layers of the biomaterial. The resulted culture systems were incubated in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% fetal bovine serum (FBS), under standard culture conditions: 37 °C, 5% CO_2, and 95% humidity.

The resulting 3D bioconstructs will be further referred as P1_MC3T3-E1, SF:PAA/GO = 10:90/0,1; P2_MC3T3-E1 – SF:PAA/GO = 20:80/0,1; P3_MC3T3-E1 – SF:PAA/GO = 30:70/0,1; P4_MC3T3-E1 – SF:PAA/GO = 40:60/0,1; and P5_MC3T3-E1 – SF:PAA/GO = 50:50/0,1.

4.2.7 In Vitro Biocompatibility Assessment

Cell morphology: The protein expression of actin was evaluated at 24 h post-seeding of MC3T3-E1 inside the SF:PAA/GO porous scaffolds by confocal fluorescence microscopy using a Carl Zeiss LSM710 laser-scanning microscope, with Zeiss 20× and 40× 0.5NA objectives. In this view, MC3T3-E1 – SF:PAA/GO bioconstructs were fixed with 4% paraformaldehyde for 8 h, and cell membranes were permeabilized with 2% bovine serum albumin/0.1% Triton X-100 solution at 4 °C for another 8 h. Next, the bioconstructs were incubated overnight at 37 °C with Alexa Fluor 546 phalloidin for actin labeling. Cell nuclei were stained with DAPI for 30 min, and the resulting labeled specimens were inspected in confocal fluorescence microscopy. Carl Zeiss Zen 2010 software version 6.0 was used for image acquisition and analysis.

Cell viability: Live/Dead fluorescence microscopy assay was employed to evaluate MC3T3-E1 cell viability in direct contact with the porous scaffolds. MC3T3-E1 osteoblasts inside SF:PAA/GO scaffolds were labeled with calcein AM and ethidium bromide to highlight both the live and dead cell populations inside the tested

bioconstructs. In this view, after 7 days of culture, cell-biomaterials systems were incubated with the staining solution prepared according to manufacturer's instructions, for 15 min at room temperature. The stained bioconstructs were analyzed by confocal fluorescence microscopy using a Carl Zeiss LSM710 laser-scanning microscope. Images were captured with Carl Zeiss Zen 2010 software version 6.0.

Subsequently, the *cell viability* of the MC3T3-E1 cells inside SF:PAA/GO scaffolds was quantitatively determined using MTT (Thiazolyl Blue Tetrazolium Bromide) spectrophotometric assay at 24 h and 7 days post-seeding [54]. In this context, all cell-biomaterials bioconstructs were incubated in 1 mg/mL MTT solution for 24 h. The resulting formazan crystals were subjected to solubilization in DMSO for 15 h at room temperature. The absorbance of the resulting solution was measured by spectrophotometry at 550 nm (Appliskan Thermo Scientific, Waltham, MA, USA). The optical densities obtained are proportional to cell viability.

Cytotoxic potential: The cytotoxic potential of the studied SF:PAA/GO composite hydrogels on the MC3T3-E1 osteoblasts was evaluated using the "in vitro toxicology assay kit lactate dehydrogenase based" according to the manufacturer's protocol [55]. Briefly, the culture media were harvested at 24 h and 7 days post-seeding and mixed with the solutions provided in the kit. After 20 min of incubation at room temperature in a dark room, the LDH concentration was determined by measuring the optic density of the resulting solutions at 490 nm (Appliskan Thermo Scientific, Waltham, MA, USA).

Statistical analysis: The spectrophotometric data were statistically analyzed using GraphPad Prism 3.03 Software, one-way ANOVA, Bonferroni test. The experiments were performed with $n = 3$ biological replicates, and each data set is presented as the average of three replicates (mean $\pm$ standard deviation).

4.3 Results and Discussions

4.3.1 Spectroscopic Characterization of the SF:PAA/GO Composite Hydrogels

The characteristic peaks of SF are amide I at 1643 cm^{-1} (C=O stretching), amide II at 1541 cm^{-1} (N–H deformation and C–N stretching), and amide III at 1256 cm^{-1}(N–H deformation and C–N stretching).

Polyacrylamide spectrum shows a sharp peak with two spikes attributed to N–H and C=O stretching. On the other hand, we can observe that the specific peak of OH and NH groups becomes large (wide) with the increases of the silk fibroin concentration in the composite materials.

The amide II and amide III specific wavenumbers from SF did not appear in the FTIR pattern of hydrogels (Fig. 1).

Additionally, the O–H and N–H bonds region presented important changes. The peak from 3294 cm^{-1}, attributed to NH stretching of the amides group from silk

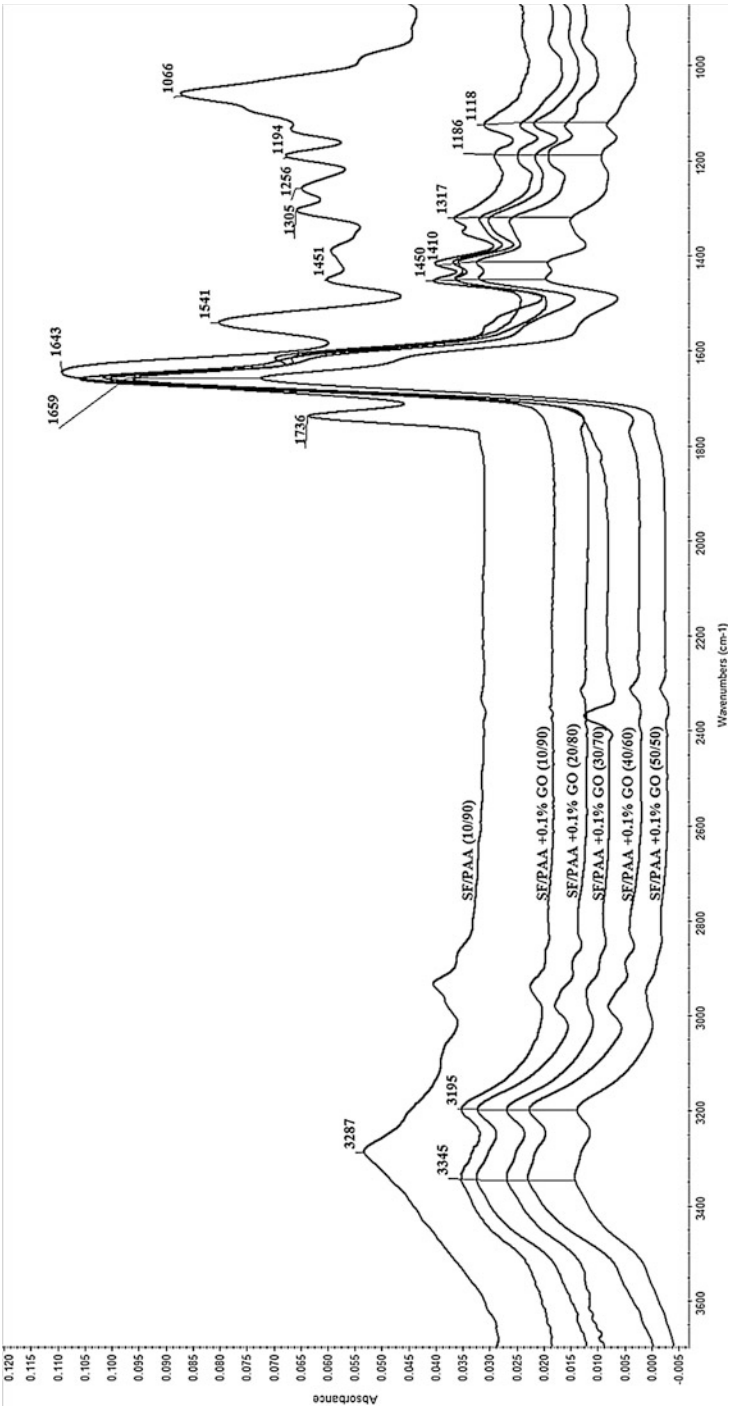

Fig. 1 The FT-IR spectra of SF/PAA hydrogel and SF/PAA/GO hydrogels with different content in SF (10/90, 20/80, 30/70, 40/60, 50/50)

fibroin implicated in forming of inter- and intramolecular hydrogen bonds, became broader, and the intensity decreased with the increase of the SF concentration. A new absorbance peak appeared at 3338 cm^{-1}, attributed to the forming of new hydrogen bonds and free amide groups as a result of broken a part of the hydrogen bonds from SF amides by addition of PAA.

SF:PAA/GO hydrogels spectra offer useful information about hydrogel structure following the major peaks: 3338 cm^{-1} NH stretching; 3188 cm^{-1} NH stretching; and 1652,1654, 1656, and 1659 cm^{-1} amide I from 10/90, 20/80, 30/70, 40/60, and 50/50 C=O stretching. The shifting of the amides is characteristic for β-sheet structure of SF within the hydrogel and could be attributed to the hydrogen – bonded from the inter-molecular hydrogen bonds between the carbonyl groups of the SF and the hydrogen donating groups of GO [56].

Raman analysis is a nondestructive technique which can provide a structural and qualitative characterization of the obtained materials [57].

In this study, Raman spectroscopy was used to determine the ordered (the G band) and disordered (the D band) crystal structure of graphene oxide [58]. The Raman spectrum of the SF-GO composite hydrogels highlights the presence of the graphene oxide sheets in the polymeric matrix (hydrogel matrix). This spectrum is characterized by three distinguished maxima (peaks) at ~1360 and ~1605 cm^{-1} attributed to the D band and the G band in graphene oxide. It can be observed a shifting of the G and D band of GO from the composite hydrogels, which can be the result of the intercalation of the polymer chain in the graphene oxide sheets [59] (Fig. 2).

4.3.2 Swelling Behavior of the SF:PAA/GO Composite Hydrogels

The swelling curves of SF/PAA/GO hydrogels with various ratio between SF and PAA (10/90; 30/70; 50/50) containing 0.1% (w/v) GO are shown in Fig. 3.

All the samples were immersed in distilled water and reached equilibrium in 50 h at 37 °C. The initial weight of the dried sample and the weight of the swollen hydrogels were used to obtain the swelling behavior of the SF/PAA/GO hydrogels. These hydrogels have semi-interpenetrating network, where the fibroin and graphene oxide are randomly distributed in the PAA network, which can generate high swelling ratio due to their relatively loose structure. It can be observed that in the first minutes the swelling degree shows an impressive increase, and after 5 h the increase is significantly reduced reaching a plateau after 50 h.

This analysis showed that the incorporation of the graphene oxide and the increasing of the SF concentration induced higher values of the swelling degree due to the increase of the hydrophilic groups of the polymer and the decrease of the cross-linking density [60].

4.3.3 SF:PAA/GO Composite Hydrogels Morphology

Freeze-dried SF structure was revealed by scanning electron microscopy (SEM) (Fig. 4).

SEM microphotographs of silk SF:PAA/GO hydrogels revealed the porous structure of these materials with different compositions. All the samples showed uniform pore distribution with opened and interconnected pores and well-defined

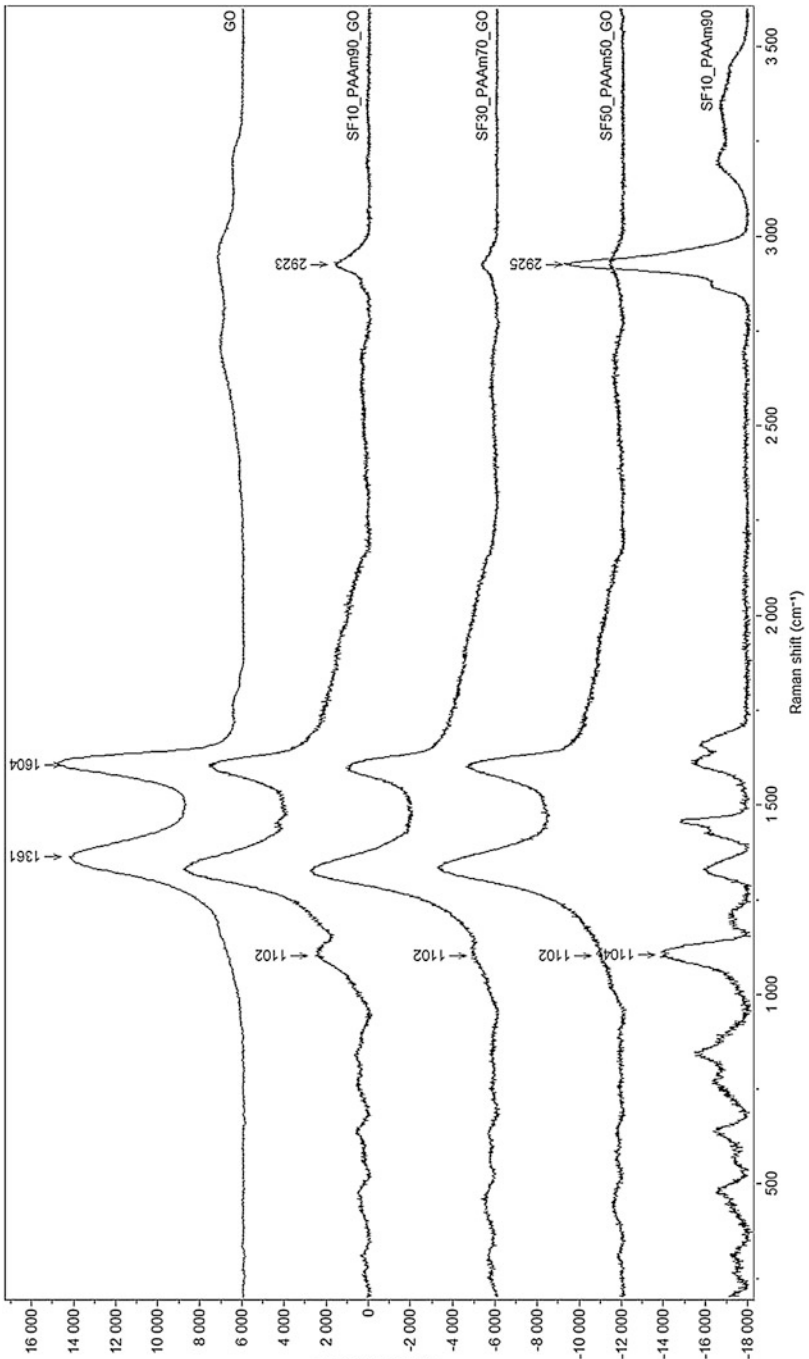

Fig. 2 The Raman spectra of graphene oxide, SF/PAA hydrogel, and SF/PAA/GO hydrogels with different content in SF (10/90, 30/70, 50/50)

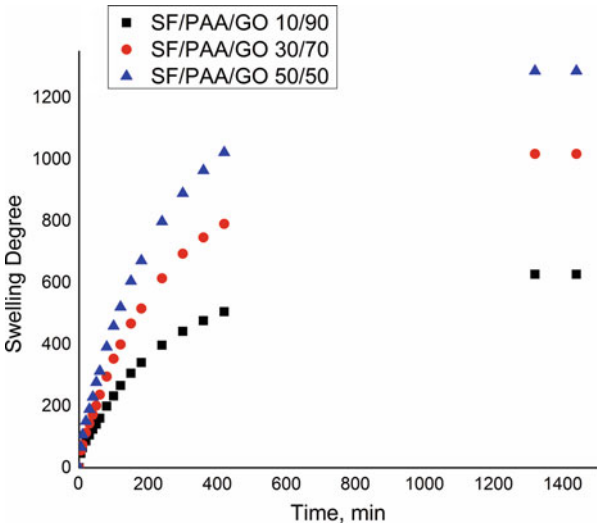

Fig. 3 Swelling degree of SF:PAA/GO composite hydrogels with different SF/PAA ratios (10/90, 30/70, 50/50)

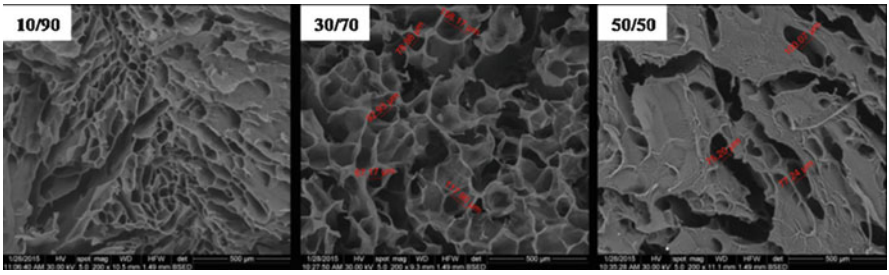

Fig. 4 Scanning Electron Microscopy images of SF:PAA/GO composite hydrogels with different content in SF (10/90, 30/70, 50/50)

circumferences. The pore size increased with the increase in silk fibroin content within the composite hydrogels due to the decreasing of cross-linking density of polyacrylamide.

4.3.4 Biomineralization Properties of the SF:PAA/GO Composite Hydrogels

The mineralization capacity in SBF 1× of the graphene oxide composite hydrogels was assessed through SEM analysis. All the hydrogels were uniformly covered with a mineral layer whose morphology strongly depended on hydrogels composition (Fig. 5). The mineral phase was composed of microglobule-type elementary features. A higher content of silk fibroin within the hydrogel (40/60 and 50/50) led to a

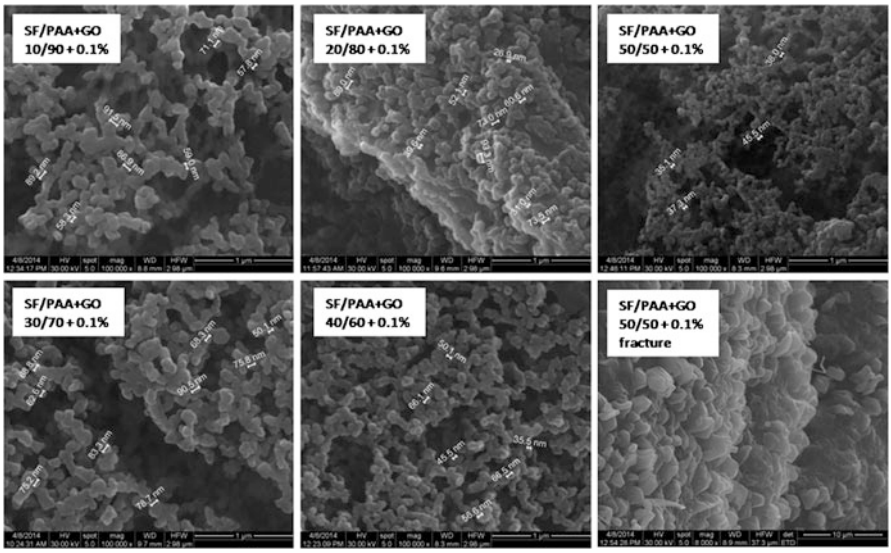

Fig. 5 SEM images of SF:PAA/GO composite hydrogels with different content in SF (10/90, 20/80, /30/70, 40/60, and 50/50_surfaceand fracture) after SBF1× biomineralization

more uniform cover of the surface with mineral phase, a higher number of microglobules and the decrease of their size.

Taguchi mineralization assay led to a more uniform coverage with hydroxyapatite both onto the surface and inside the hydrogels (Fig. 6, surface and fracture analysis). The role of silk fibroin on the mineralization ability of the hydrogels is very important together with the carboxyl groups from graphene oxide, but the composition did not influence the materials behavior in this alternate soaking solutions.

4.3.5 SF:PAA/GO Composite Hydrogels Biocompatibility

MC3T3-E1 Osteoblasts Morphology Inside SF:PAA/GO Composite Hydrogels

MC3T3-E1 osteoblasts morphology inside SF:PAA/GO composite hydrogels and their ability to interact with the substrate material in terms of adhesion and cytoskeleton development were investigated after 24 h of culture. As shown in Fig. 7, MC3T3-E1 cells displayed long and distinctive actin filaments surrounding the nuclei inside SF:PAA/GO = 30:70/0,1; SF:PAA/GO = 40:60/0,1; and SF:PAA/GO = 50:50/0,1. This distribution of the cytoskeleton components clearly determined cell overall elongated morphology inside the scaffolds with high fibroin content. Unlikely, MC3T3-E1 osteoblasts inside SF:PAA/GO = 10:90/0,1 and SF:PAA/GO = 20:80/0,1 displayed short actin filaments surrounding the nuclei and the overall cellular shape was round.

Actin microfilaments formation may be assigned with a shape modeling process that occurs in response to the direct contact of the cell with the biomaterial. The actin

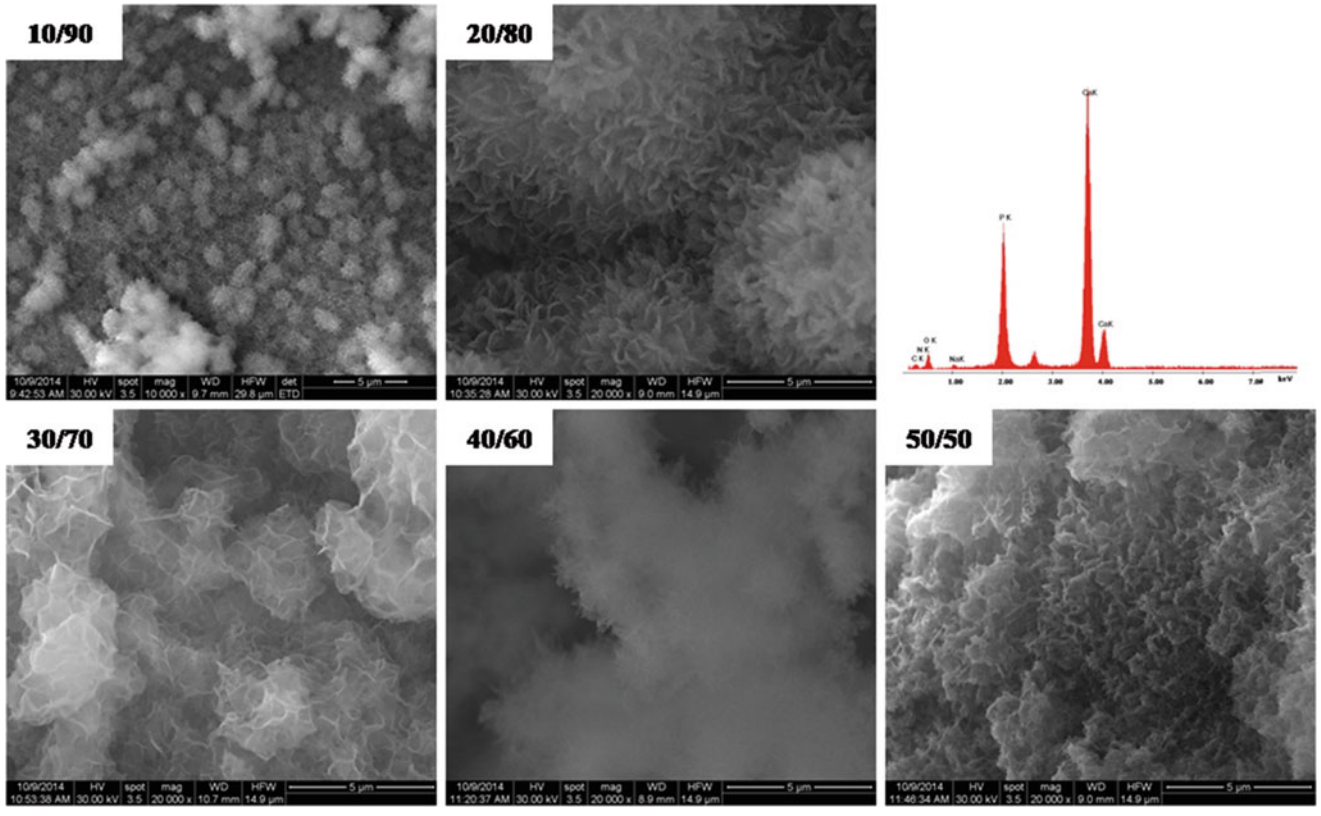

Fig. 6 Scanning Electron Microscopy images of SF:PAA/GO composite hydrogels with different content in SF (10/90, 20/80, /30/70, 40/60, and 50/50_surface and fracture) after biomineralization in alternating soaking solutions

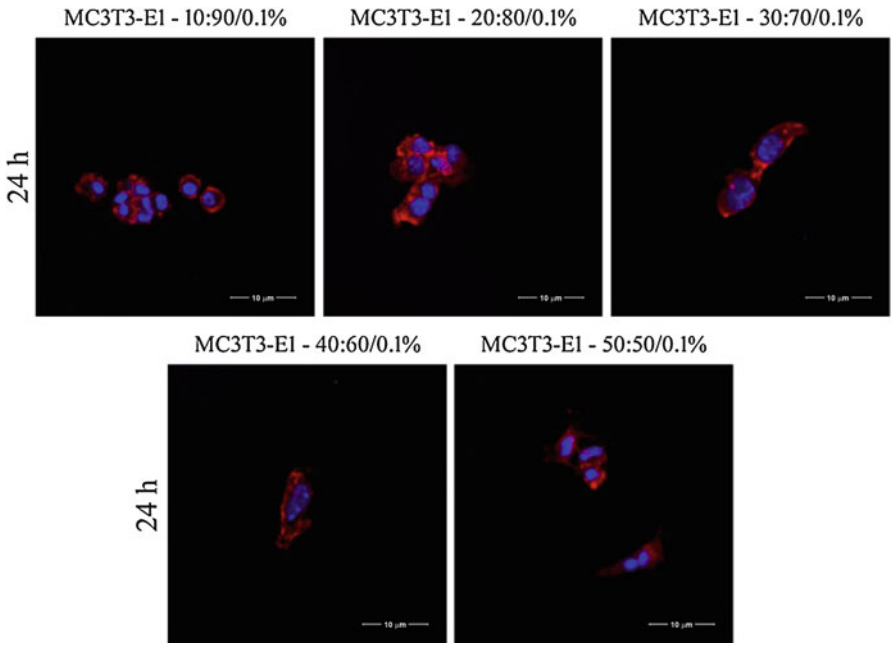

Fig. 7 Confocal fluorescence microscopy micrographs of MC3T3-E1 osteoblast actin filaments network (red fluorescence) in P1–5 bioconstructs; DAPI-stained nuclei are blue

cytoskeleton underlies the cell adhesion process, which is highly important for further tissue formation. In this context, our results suggest that the natural silk fibroin component of the tested composite hydrogels might be crucial for MC3T3-E1 preosteoblast adhesion to the proposed scaffold.

MC3T3-E1 Osteoblast Viability Inside SF:PAA/GO Composite Hydrogels

LIVE/DEAD Fluorescent Microscopy Assay

In order to examine cell survival inside the tested biomaterials, the viability of MC3T3-E1 cells was evaluated at 7 days post-seeding by confocal fluorescence microscopy (Fig. 8), based on the simultaneous staining of live (green labeled) and dead (red labeled) cells.

As shown in Fig. 8, the ratio between the living and dead cells was always positive for all the tested compositions. Although significant differences were noticed with respect to the cell density inside the scaffolds, the amount of green living cells increased with the concentration of silk fibroin. Consequently, the highest amount of living MC3T3-E1 cells was found in MC3T3-E1 – SF:PAA/GO = 40:60/0,1 and MC3T3-E1 – SF:PAA/GO = 50:50/0,1.

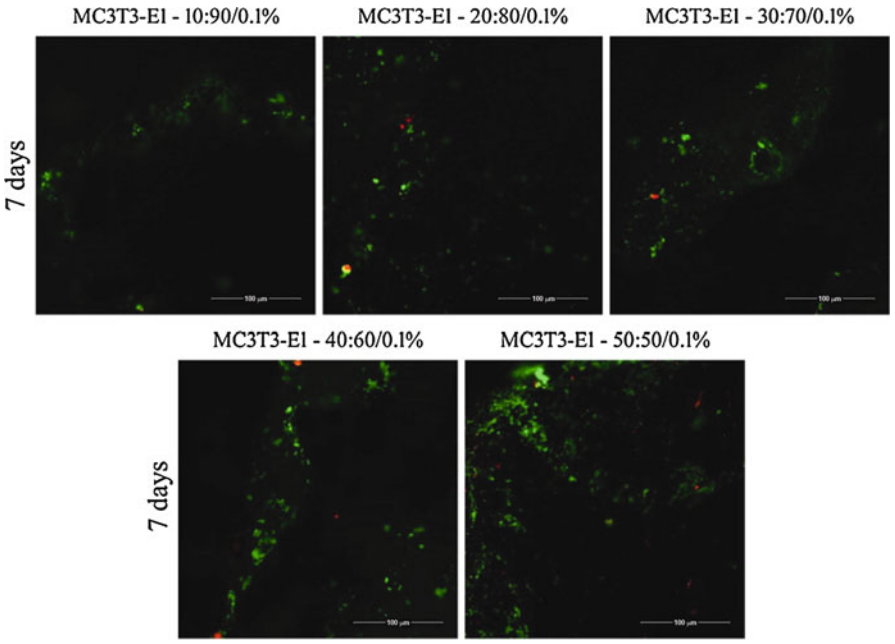

Fig. 8 Confocal fluorescence microscopy micrographs revealing live and dead cells inside P1–5 bioconstructs, after 24 h of culture. Green, living cells; red, dead cells

Together with the cell morphology observations, these results might suggest that silk fibroin protein plays a crucial role in the design of the biosystem as it supports cell adhesion and cell proliferation. Furthermore, silk fibroin concentration might be crucial for the scaffold's biocompatibility.

MTT Assay

MC3T3-E1 osteoblast viability inside all the SF:PAA/GO compositions was quantitatively determined by MTT spectrophotometric assay. In this context, the P1, P2, P3, P4, and P5 biohybrids were subjected to MTT spectrophotometric assay at 24 h and 7 days of culture. The results were graphically represented in Fig. 9 after the statistical analysis in GraphPad Prism 3.03.

MC3T3-E1 cells survived inside all the tested compositions after 7 days of culture. Significant differences were detected in terms of cell viability between the tested compositions $*p < 0.05$ [P1 vs. P2 and P2 vs. P3 at 24 h post-seeding] and $***p < 0.001$ [P3 vs. P4 at 24 h post-seeding]. No significant differences were detected between P4 and P5 at 24 h post-seeding, suggesting that both compositions equally support cell viability. Additionally, MC3T3-E1 cells inside P4 and P5 scaffold displayed the highest viability both at 24 h and 7 days post-seeding, confirming with the fluorescent microscopy observations.

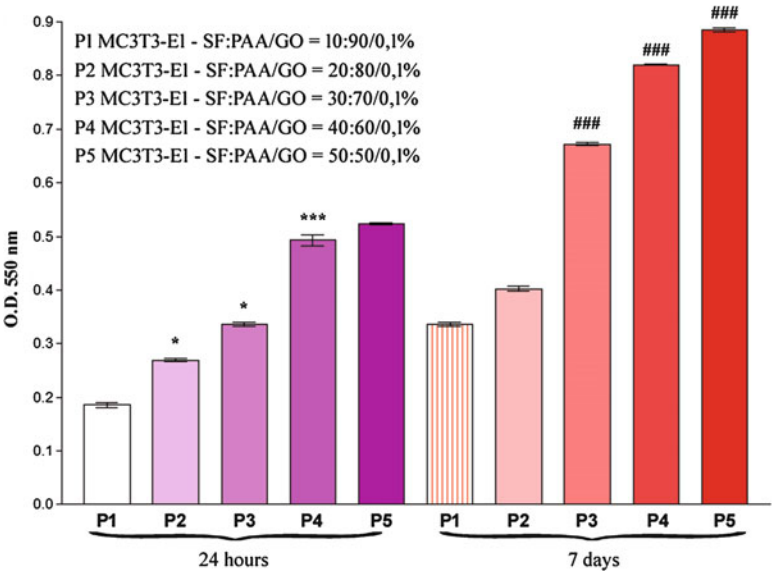

Fig. 9 Quantification of MC3T3-E1 cell viability inside SF:PAA/GO = 10:90/0,1; SF:PAA/GO = 20:80/0,1; SF:PAA/GO = 30:70/0,1; SF:PAA/GO = 40:60/0,1; and SF:PAA/GO = 50:50/0,1 scaffolds, as revealed by MTT test at 24 h and 7 days post-seeding. *p <0.05 [P1 vs. P2 at 24 h post-seeding; P2 vs. P3 at 24 h post-seeding]; ***p <0.001 [P3 vs. P4 at 24 h post-seeding]; ###p <0.001 [P3 at 24 h post-seeding vs. P3 at 7 days post-seeding; P4 at 24 h post-seeding vs. P4 at 7 days post-seeding and P5 at 24 h post-seeding vs. P5 at 7 days post-seeding]

Regarding the proliferation status of the MC3T3-E1 cells inside the tested composition, only inside P3, P4, and P5 scaffolds, the cellular viability was significantly increased at 7 days of culture as compared to 24 h post-seeding (###p <0.001) These results suggest that the MC3T3-E1 osteoblasts proliferated only inside P3, P4, and P5 composite hydrogels.

Biomaterials' Cytotoxic Potential on MC3T3-E1

The cytotoxic potential of P1, P2, P3, P4, and P5 scaffolds was evaluated by spectrophotometric quantification of the LDH enzyme release in the culture media by MC3T3-E1 cells seeded inside the samples. The results were graphically represented in Fig. 10 after the statistical analysis in GraphPad Prism 3.03.

LDH activity in the culture media significantly decreased statistically both at 24 h and 7 days post-seeding with the increase of the silk fibroin content in the formulation of the hydrogels (*p <0.05 [P3 vs. P4]; ***p <0.001 [P1 vs. P2 and P2 vs. P3]). This finding, together with the observations mentioned above, might suggest that the scaffolds do not exert a cytotoxic effect on cells and at low concentrations of silk fibroin do not allow cells to adhere and proliferate.

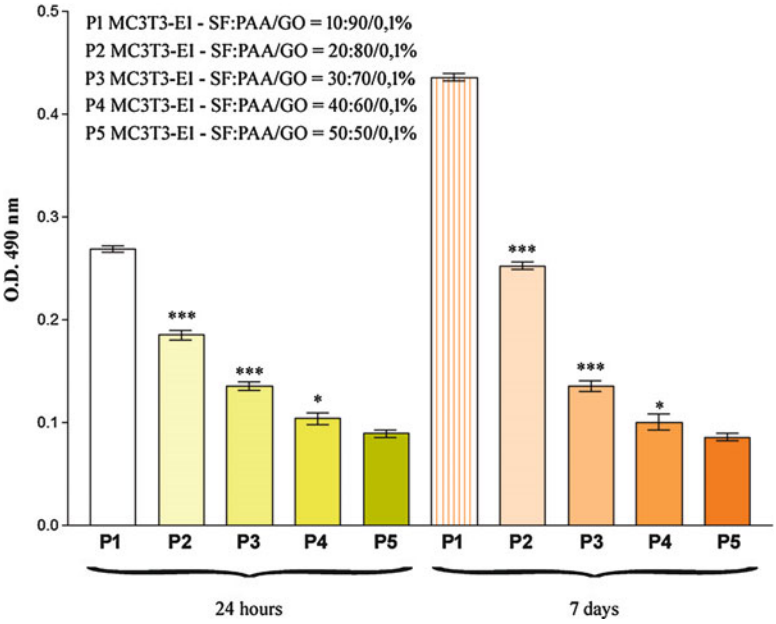

Fig. 10 Quantification of SF:PAA/GO = 10:90/0,1; SF:PAA/GO = 20:80/0,1; SF:PAA/GO = 30:70/0,1; SF:PAA/GO = 40:60/0,1; and SF:PAA/GO = 50:50/0,1 scaffolds cytotoxic potential on MC3T3-E1 cells as revealed by the LDH assay at 24 h and 7 days post-seeding. *p <0.05 [P3 vs. P4 at 24 h and at 7 days post-seeding]; ***p <0.001 [P1 vs. P2 at 24 h and at 7 days post-seeding and P2 vs. P3 at 24 h and at 7 days post-seeding]

5 Conclusion

Osteoblast morphology varied in the tested compositions, and our data suggest that silk fibroin significantly improved the cytoskeleton organization and distribution inside the cells. The viability and proliferation data together with the quantification of the cytotoxic potential suggested that the murine osteoblasts proliferate more in contact higher content of silk fibroin, most probably due to the better adhesive properties of the composites and not to potential cytotoxic effects. Consequently, the SF:PAA/GO = 40:60/0,1 and SF:PAA/GO = 50:50/0,1 biocomposites proved to be biocompatible and displayed the most equilibrated ratio between the pro-proliferative and cytotoxic potential. The excellent biocompatibility, good mechanical properties, and biomineralization potential recommend the proposed formula as a remarkable biomaterial, with potential in biomedical applications such as bone regeneration.

In spite of the promising results mentioned earlier, there are still some important issues to be addressed in the future. First, the potential long-term toxicity and the

non-biodegradability of graphene should be further investigated. Second, the specific effects of graphene on cells, tissues, or organs and their metabolic pathway in vivo remain unclear and require further studies.

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