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Mohd Shabbir *Editor*

Regenerated Cellulose and Composites

Morphology-Property Relationship

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Preface

Exhaustive utilization of petroleum resources and synthetic materials parallelly invested to the climate change and subsequently rise in temperature has been a concern of present time. Products from natural resources are best alternatives of all time, natural polymers play a major role to that. Being the most abundant natural polymer on earth and gateway to large number of applications, cellulose is expected to be explored for higher efficiencies. Challenging part, i.e., dissolution of cellulose, has been explored and several solvents already there. Since morphology of the materials is the key feature and corresponds to associated application to the materials, it is highly needed to assimilate the literature on morphology-property relationship of cellulose materials. This book will try to accumulate all such literature relying on morphology-property relationship of cellulose materials and will give direction to the ongoing research to this relationship. This effort, with the help of eminent authors around the globe with the expertise in related research areas, is expected with a great research outcome in regenerated cellulose chemistry and research.

This book is composed of 12 chapters from various research areas dealing with morphological aspects of regenerated cellulose and characteristic applications of various morphologies. Introduction chapter overviews the dissolution of cellulose and regeneration into various morphologies. Cellulose dissolution and regeneration are explored in detail in the second chapter in view of green chemistry approaches. Further, the regeneration into morphologies such as spherical, sheets, membranes, and films is discussed in the next chapter including recent advances in this area. Surface modifications of regenerated cellulose materials are reviewed in the fourth chapter. Cellulose can be modified via organic and inorganic means that are discussed in detail. The fifth chapter is dedicated to nanocellulose materials and their applications in several fields. Next chapter in continuation discussed spherical morphologies of cellulose, specifically microspheres and beads, their fabrication, and applications. Regenerated cellulose materials modified with functional groups play important role in chromatographic separation of compounds. The seventh chapter is dedicated to the chromatographic separation through cellulose. Next two chapters explored energy applications, textiles, and food applications of regenerated cellulose. From textile fibers to conducting materials are discussed in these chapters. Last group of

chapters reviewed pharmaceutical and biomedical applications. Drug delivery, wound dressing, tissue engineering, dentistry, etc., are discussed through them.

The book *Regenerated Cellulose and Composites—Morphology-Property Relationship* contains informative chapters from the authors of their specialized fields about cellulose and its applications in various sectors. I hope that students, researchers, and academicians of fields such as materials science, chemical engineering, environmental science, textiles, and food industry will find this book of great interest and useful in their curriculum. This book will definitely be helpful for emerging new ideas in cellulose research leading to interdisciplinary research collaborations.

Now it comes to thank those who had been a support to this book in any way. I acknowledge the great efforts of the eminent authors without whom this book was not imaginable, and my family members, colleagues, and students. I appreciate the support of the publisher to show interest and let me compile this referenced book.

Greater Noida, India Mohd Shabbir

Contents

An Introduction to Regenerated Cellulose: Morphologies and Applications

Fehmeeda Khatoon, Mohd Shabbir, and Annu

Abstract Being one of the most abundant materials on earth, cellulose has attracted attention for the practical applications. Since the methods to dissolve and regenerate cellulose have been evolved, the momentum of utilizing the compact nature of cellulose via transformation into various morphologies is accelerated. As the morphology-specific applications are evolved, various methods of transforming regenerated cellulose into various morphologies are developed. From nanocellulose to cellulose beads, hydrogels, fibers, sheets or membranes, microspheres, etc. have been developed and used for several applications such as wastewater treatment, sensing, drug delivery, tissue engineering, wound dressing, separation, catalysis, and energy. This chapter is to introduce the cellulose regeneration and molding into various morphologies for specific applications.

Keywords Cellulose · Nanocellulose · Microspheres · Drug delivery · Wastewater treatment · Energy

1 Introduction

Cellulose is one of the most abundant biopolymers on this planet. Plants and some bacteria synthesize and produce cellulose. It is a homopolymer of glucose, and monomers are linked by β-1,4 linkages (Fig. 1). Cellulose is a tough, fibrous polysaccharide and insoluble in water solvent. Cellulose is responsible for the compact and stable structure of plant cell walls. Cellulose chains are arranged in microfibrils, and

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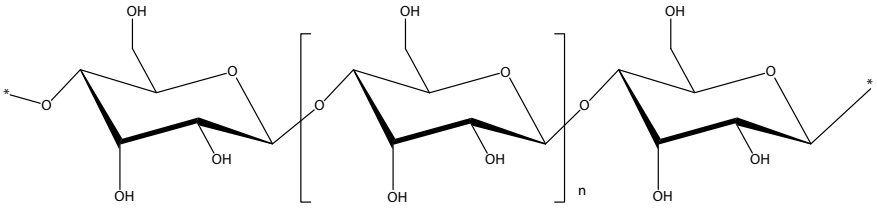

Fig. 1 Cellulose chemical structure

microfibrils arranged in fibrils are bundles of them and ultimately make up the plant cell wall. Polymeric chains are bound to each other via H-bonding in layers. This arrangement provides the strength and superior mechanical properties to cellulose biopolymer. Cellulose is not only synthesized in plants, but also be produced by some bacteria, and it is of high purity and crystallinity unlike it is separated from lignin in case of plants [1].

Cellulose dissolution has been a great challenge to utilize and process for practical applications. Arrangement of polymeric chains and interactions between them, mainly H-bonding, is difficult to weaken and hence the dissolution. Various solvents are used to regenerate cellulose into materials of use. The amine oxides were used to regenerate cellulose into fibers and used in textiles, construction industry. Viscose rayon and lyocell fibers were obtained via dissolution of cellulose into amine oxides such as N-Methylmorpholine N-oxide (NMMO) [2]. Solvents for cellulose dissolution and regeneration methods help in deciding morphology of the regenerated cellulose. Various morphologies of cellulose and their characteristics along with applications are introduced in this chapter.

2 Nanocellulose

Nanocelluloses (NCs) are usually isolated or produced from cellulose fibers of agricultural residues via different methods, and these may include chemical, mechanical, hydrolysis (acid or enzymatic), oxidation, etc., and can also be produced by bacteria from glucose (Fig. 2). NCs can be classified into three categories, that are cellulose nanocrystals (CNCs), nanofibrillated cellulose (NFCs), and bacterial nanocellulose (BNCs) depending on the morphological features, functions, and preparation methods of NCs. CNCs and NFCs are generally obtained via a top-down approach consisting of the disintegration of plant matter, while synthesis of BNCs follows bottom-up approach using cultures of bacteria [3–5].

The removal of amorphous regions by hydrolysis (acidic or enzymatic) from cellulose fibers usually give CNCs. They are of high purity rod-like or whisker shape cellulose crystals having diameters and lengths in nanoscale sizes. Flexibility is reduced relatively in these types of NCs due to the removal of amorphous regions in the structure [7–9]. Aggregation of long thread-like bundles of cellulose chain

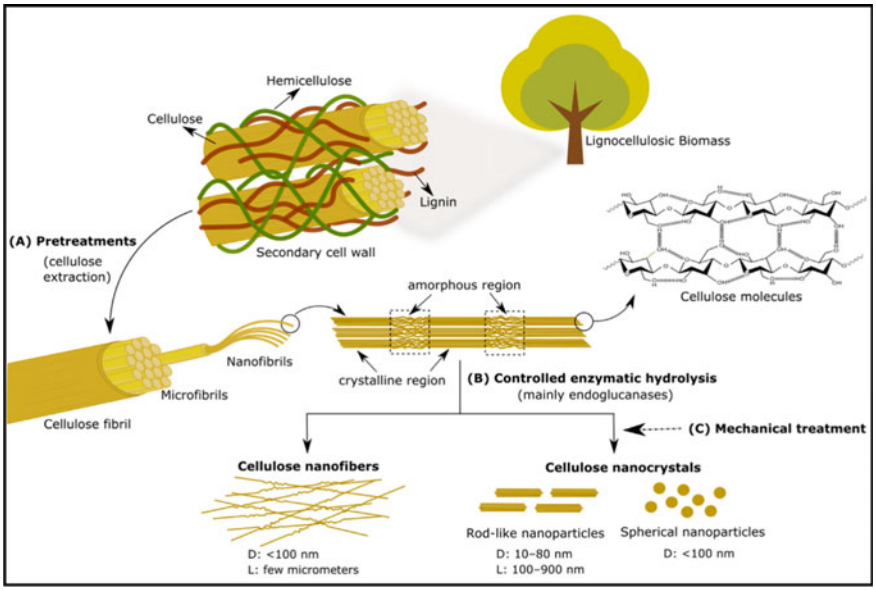

Fig. 2 Production of nanocellulose, pretreatments, and enzymatic hydrolysis [6]

molecules with flexible, long, and entangled cellulose nanofibers (CNFs) forms NFCs. They are equipped with less than 100 nm diameter and several micrometers length and also called as nanofibrils, nanofibrillar, and nanofibers made of cellulose. NFCs are usually generated/extracted through the mechanical disintegration processes, by using electrospinning technique. NFCs have a high aspect ratio and, unlike CNCs, contain both crystalline and amorphous regions and exhibit a web-like structure [10, 11]. Third category, i.e., bacterial nanocelluloses (BNCs) or bacterial cellulose (BC) is composed of continuous 3D network of CNFs, usually produced as hydrogels or nanofilms via "bottom-up" synthetic routes by synthesizing cellulose from carbon sources such as glucose in the aqueous culture media of specific bacteria such as *Gluconacetobacter xylinus*. These nanocelluloses demonstrate better purity, crystallinity, and mechanical stability compared to the CNCs and NFCs [12, 13]. Nanocelluloses find its applications in various fields including biomedical, food packaging, reinforcements, bioplastics, optics, adhesives, coatings, and engineering (Fig. 3).

3 Cellulose Beads and Microspheres

Spherical morphology of regenerated cellulose is studied into two categories depending on the size range. If the size range of materials is in micrometers (up to 500 μm), then they are included in category microspheres, and if this size range

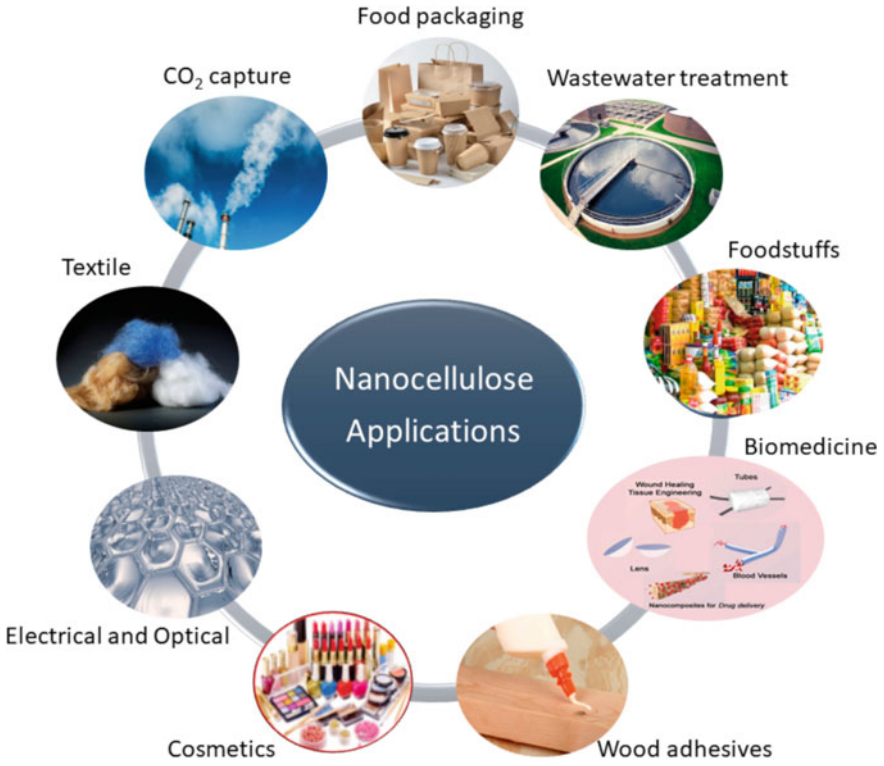

Fig. 3 Various application areas of nanocellulose [14]

extends further, materials are categorized as beads. Regenerated cellulose microspheres or beads are designed usually porous to enhance the active surface area. Dispersion method is generally opted for microspheres formation, in which cellulose is dissolved in solvent first, and then, emulsion is made. Dispersed phase particles' size can be controlled by the speed of mixing the emulsion. Once the optimum size achieved the dispersed phase, solidification of dispersed phase via solvents of different polarities is carried out. While cellulose beads are of size greater than 500 μm and are designed by dropping and solidifying them in their sizes, depending on the pore size of syringe, size of the cellulose beads can be regulated [15, 16].

Owing to the spherical morphology (Fig. 4) of these materials, they are highly used for adsorptive removal of pollutants from wastewater, drug delivery systems, catalysis, and chromatographic separation applications [18, 19]. Various surface modifications are carried out for higher efficiencies of regenerated cellulose and act as a carrier for particular compounds. High surface area of spherical morphology leads to higher adsorption, and porous nature of these materials also enhances that surface area and ultimately the efficiency of adsorptive removal of pollutants from wastewater. Sometimes, to adsorb specific ions or molecules, surface modifications are carried out accordingly. Photocatalytic materials can also be embedded into regenerated

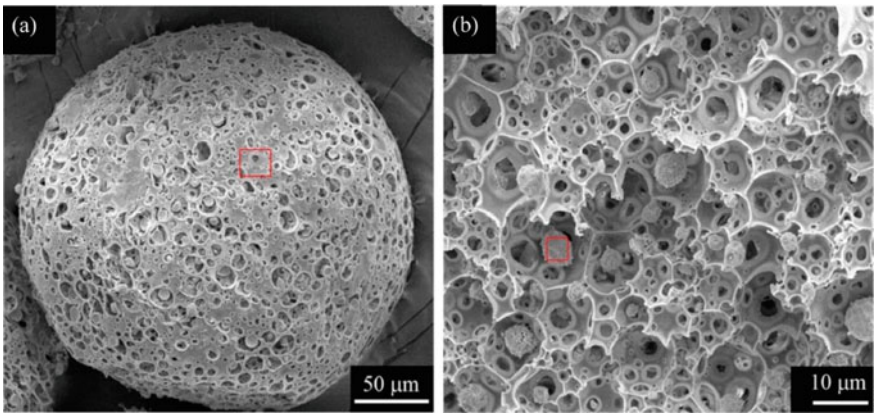

Fig. 4 Cellulose-based microspheres and their porous structure [17]

cellulose microspheres for catalytic degradation of organic pollutants such as dyes or pharmaceuticals [20, 21].

4 Cellulose Fibers

Cellulose fibers have been used in our daily lives for long. They are widely used for clothing purposes. Common regenerated cellulose fibers used for clothing are rayon and fabricated by viscose process; cellulose is converted into the cellulose xanthogenate and spun into fibers. Rayons are usually of three types that are regular rayon, high wet modulus rayon, and high tenacity rayon, and regular rayon (Viscose® rayon) has the largest market share among them. Viscose solution is prepared by reacting cellulose with NaOH and then with CS2 to get cellulose xanthogenate, and then, it is forcefully passed through a spinneret into acidic coagulating solution to generate regenerated cellulose filaments [22]. Cuprammonium rayon is another commercial regenerated cellulose fiber fabricated by cellulose dissolved in cuprammonium solution. Copper and ammonia are removed by treating with coagulating solution. By varying the solvents, several chemical modifications, and methods of manufacturing, regenerated cellulose fibers of varying characteristics have been obtained with different names [23, 24].

5 Cellulose Membranes and Sheets

Cellulose is also developed into membranes and sheets commonly by casting method. Cellulose is dissolved into solvents first and then casted on flat surface such as glass, and thickness of the membranes can be maintained in this step. Casted cellulose is regenerated by treating it with coagulating solution, generally acidic solutions

such as H_2SO_4. The concentration of the cellulose solution and the coagulation temperature control the porosity and pore size of the membranes [25]. Vacuum filtration, solution regeneration, electrospinning, phase inversion, etc. are other methods for the preparation of cellulose membranes. Regenerated cellulose membranes are used for various applications in food packaging, water treatment, cosmetics, medicals/pharmaceuticals packaging, and sensing. Several organic and inorganic components (metal nanoparticles, fluorophores, organic dyes, and antigen-antibodies) are introduced into cellulose to design for specific use of membranes [22, 26].

6 Cellulose Hydrogels and Scaffolds

Hydrogels are three-dimensional network structures formed of polymeric chains held via physical and chemical cross-linking. Hydrogels have tendency to absorb and retain large amounts of water in their interstitial structures, maintained by the interactions responsible for the unique 3D structure. Physical and chemical interactions of polymeric chains also help in preventing the dissolution in solvents and swelling during water absorption while maintaining structure. Water absorbing tendency is due to the presence of hydrophilic groups such as—OH, –COOH in their 3D structure. Cellulose-based hydrogels are fabricated from pure cellulose solution by physical cross-linking of the chains owing to the hydroxyl groups in cellulose structure. Hydrogen bonding is the primary force to hold polymers into network structures [27]. These hydroxyl groups can also attract various interactions toward other moieties or derivatization of cellulose and resulting into cellulose composite hydrogels. Cellulose hydrogels are well-known structures for their swelling and mechanical properties. Owing to these characteristics, hydrogels find their application area in biomedical fields (drug delivery, wound healing, tissue engineering), textiles, agricultural fields, etc. These promising aspects of cellulose hydrogels make their studies important for researchers and scientists [22, 28].

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Green Chemistry Approaches to Cellulose Dissolution and Regeneration

Woan Qian See, Jamarosliza Jamaluddin, Norazah Basar, Noor Fitrah Abu Bakar, Amizon Azizan, Muhd Nazrul Hisham Zainal Alam, Jau Choy Lai, Mohd Asmadi, and Nadia Adrus

Abstract The dissolution of cellulose is a critical step for the efficient conversion of the cellulose into a high added value product. Yet, so far, attention had been paid mostly to the conventional solvents such as *N*,*N*-dimethylacetamide/lithium chloride (DMAc/LiCl). Therefore, initiatives to develop highly efficient and green cellulose solvents can broaden the cellulose regeneration for various applications. Dissolution of cellulose in green solvents allows the comprehensive utilization of cellulose by combining the green chemistry principles involving the usage of environmentally preferable solvents. Green solvents including ionic liquids (ILs) and deep eutectic solvents (DESs) have played unique roles in the cellulose dissolution. ILs are novel green and attractive solvents due to their favorable properties. ILs with high thermal stability, nearly non-volatility, and structural diversity consequently show an outstanding capability for dissolving cellulose. In addition, deep eutectic solvents (DESs) with unique physicochemical properties, has emerged as green alternative to ILs, have shown considerable potential as versatile solvents for cellulose dissolution. Herein, this chapter underlines a more appropriate dissolution mechanism and provides an insight into the effectiveness of cellulose dissolution in the ILs and DESs.

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1 Introduction to Green Solvents

Solvents are used in many important chemical processes, especially fine chemical manufacturing. The toxicity and flammability of the conventional solvents used in wide range of industrial and domestic applications provide a great challenge to green chemistry. Since the introduction of "the 12 Principles of Green Chemistry" in 1998, as one of it explicitly claims the use of "safer solvents and auxiliaries", there has been a persistent attempt to replace conventional solvents with more environmentally friendly alternatives [1].

Green solvents are one of the most important ways to express the goal of minimizing environmental effect in a variety of industrial applications for long-term development. A chemical production process's sustainability can be significantly improved by selecting the right solvent for the operation. Figure 1 shows the general characteristics of green solvents.

Water is the best solvent of all green solvents since it is abundant in nature. It is non-toxic to human health and the environment, easily available, and has a high specific heat capacity. Ionic liquids (ILs) and deep eutectic solvents (DESs) have emerged as promising green solvents because of their low vapor pressure *and* high chemical and thermal stability, which offers advantages such as ease of containment, product recovery, and recycling ability [2]. Meanwhile, liquid polymers have been established as solvents for catalytic reductions to avoid the inactivation of air-sensitive catalysts [3]. Biosolvents derived from renewable feedstocks are used as an alternative to hazardous petroleum solvents like hexane in extraction of oils [2]. Among supercritical fluid, carbon dioxide is the most commonly utilized because it is harmless, incombustible, widely available, and inexpensive. Its properties can be controlled by altering the temperature and pressure, and it can be easily removed from the extract by relaxing the conditions to room temperature and pressure [4]. Different types of green solvents are shown in Fig. 1b. It should be noted that each of the green solvents has benefits and drawbacks that must be considered before selecting one for a specific application.

Green solvents are utilized for a variety of functions and are used in wide range of applications. It can be used as a solvent in biocatalytic processes, extraction and purification of bioactive compounds [5]. Fundamental and industrial applications of green solvents have been applied in reaction synthesis including lipase-catalyzed reactions, organic synthesis and esterification reactions, oil extraction, sensors and biosensors, lignocellulosic biomass utilization, and bio-based chemicals. In petroleum industry, green solvents are used in extractive desulfurization (EDS) process to reduce SO2 emissions [6]. There are an increasing number of publications dealing with the use of green solvents to dissolve and increase the processability of renewable natural biopolymers in the biomedical area. The usage of green solvents in several areas is depicted in Fig. 1c.

This chapter covers the use of ionic liquids (ILs) and deep eutectic solvents (DESs) as two types of designable green solvents [7] that are used in cellulose dissolution application. Ionic liquid is a liquid molten salt made up of organic cations and organic

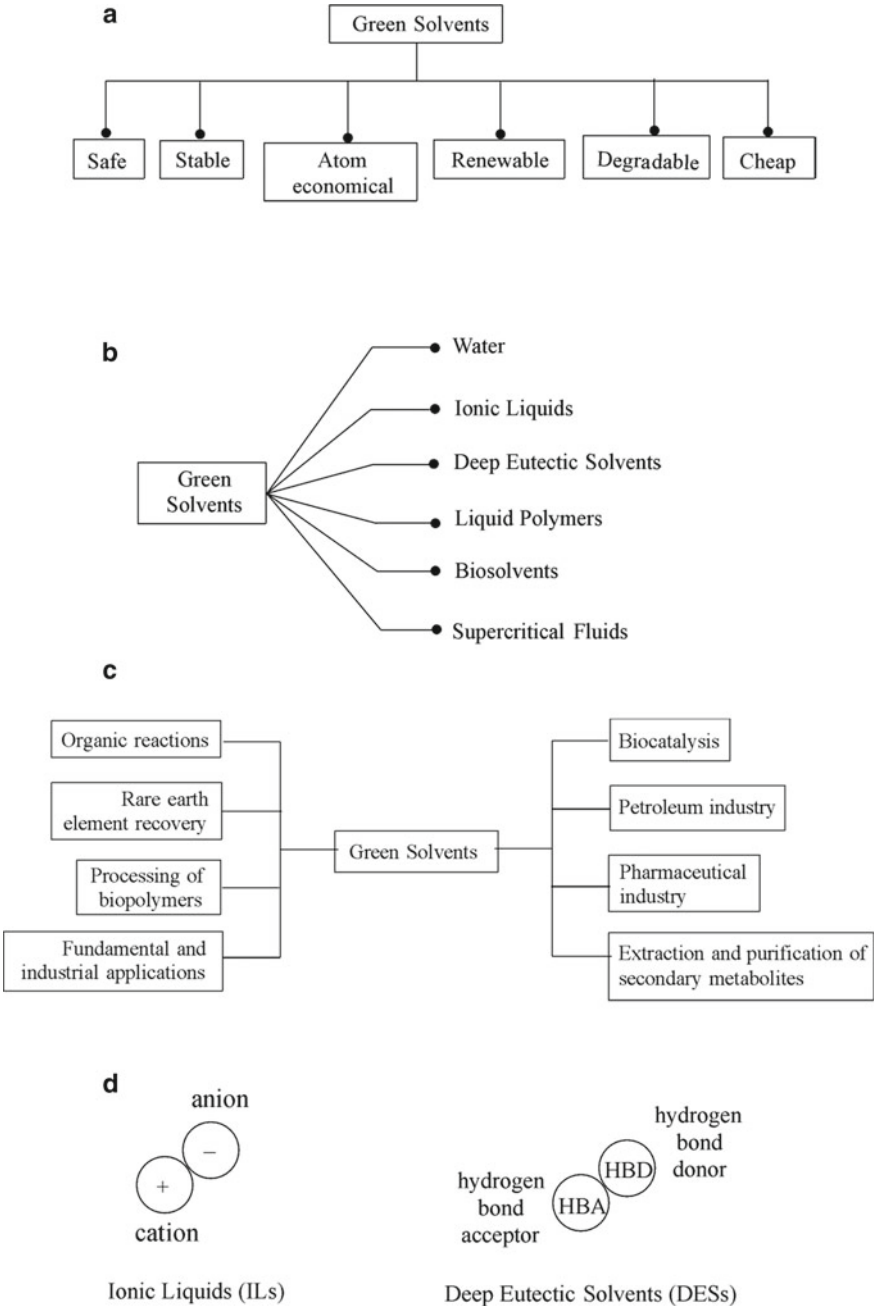


Fig. 1 **a** Characteristics of green solvents. **b** Different types of green solvents. **c** Applications of green solvents. **d** Green solvents from ionic liquids and deep eutectic solvents

or inorganic anions that melt below 100°C. DESs, a subclass of ILs, are made by mixing solid compounds to generate an eutectic mixture with a melting point lower than either of the individual components. This is due to the formation of intermolecular hydrogen bonds between the hydrogen bond acceptor (HBA) and the hydrogen bond donor (HBD) (Fig. 1d).

2 Cellulose Dissolution and Mechanism

Cellulose is the most ubiquitous natural biopolymer, accounting for half to one-third of all plant tissues [8]. Further, cellulose is a homopolysaccharide made up of long chains of D-glucose units connected by β-1, 4-glycosidic bonds [9]. Moreover, the presence of hydrophobic carboxyl groups and a plentiful hydrophilic hydroxyl group in the backbone of cellulose illustrates the amphiphilic nature of cellulose [10]. Cellulose has gained prominent assurance for a wide range of applications due to its unique properties. However, cellulose is a long polymer that is insoluble in most organic solvents due to its tightly packed crystalline structure [11]. Therefore, good dissolution is required to transform the cellulosic into high-value products.

Theoretically, cellulose dissolution is a process of hydrogen bond breaking, especially in the crystalline regions. Several definitions of cellulose dissolution have been proposed, while [12] defined it as the solvent's capability to break the inter- and intramolecular hydrogen bonds between the molecules of the biopolymer. The derivatizing solvents chemically react with hydroxyl groups and reduce the hydrogen bond network; the non-derivatizing solvents destroy inter- and intra-molecular hydrogen bonds either by hydrogen bond formation between one or more components of the solvent systems and the hydroxyl groups of the cellulose or by coordination bond formation between the metal ion present in the medium and the hydroxyl group of cellulose molecules [13, 14]. In general, the solvent's capacity is important in breaking the hydrogen bond network during cellulose dissolution. Nonetheless, hydrophobic interactions between solvent and cellulose have been suggested to play a substantial role in its dissolution due to the amphiphilic nature of cellulose [15–17].

Xu and Zhang [18] show that during the dissolution process, the crystalline structure of cellulose is destroyed. According to [12], completed dissolution is achieved when the supramolecular structure is completely destroyed, resulting in a solution in which the polymer is molecularly dispersed. On the other hand, crystallinity and associated constrained accessibility are the only inhibiting factors in cellulose dissolution [19]. It has been proposed that dissolution process may disrupt the unknown long-range ordering or interaction, thereby limiting cellulose dissolution. Studies on the dissolving of cotton fibers under stress reveal that there is not sufficient for cellulose chains to be non-crystalline but, rather, cellulose chains must exhibit local conformational motions that lead to chain disentanglement [20–22]. The research found that interactions that effect disentanglement may be distinct. As a result, the processes of decrystallization and chain disentanglement are intertwined in the breakdown of

semicrystalline cellulose. And thus, the total kinetics of dissolution is determined by their balance [23].

The dissolution of cellulose includes several stages consisting of solvent diffusion, swelling, cellulose decrystallization, chain disentanglement, and diffusion of disentangled chains towards the bulk solution, as shown in Fig. 2a. During the dissolution, the solvent diffuses into the structure of the cellulose to affect both the amorphous and crystalline regions. Succeeding the solvent diffusion into the solid cellulose [24] proposed that the solvent-cellulose interactions are capable of overcoming the strong molecular forces between cellulose chains. Meanwhile, this could enhance the probability of conformational chain motion as the crystalline network of cellulose is gradually broken down. Hence, it resulted in the transformation of cellulose into a gel-like medium as well as the swelling of the cellulosic particles [25, 26]. Swelling is the process where the solvents penetrate the cellulose structure by interacting with the polymer to a certain extent, leaving the physical properties and volume of the biopolymer significantly changed while the solid or semi-solid state remains practically unchanged [27]. However, the swelling process cannot dissolve the cellulose.

Due to the difference between chemical and stereochemical design, cellulose will experience different inter-chain forces that are responsible for maintaining the chain in the solid state [27]. The crystallinity and polar groups that may take part in the hydrogen bonding thus play a major role in the solubility and reactivity of cellulose. Therefore, cellulose decrystallization and chain disentanglement are both involved in the dissolution of semicrystalline cellulose [24]. High diffusivity and effective solvent disrupt the crystalline network of the cellulose molecules and disentangle the cellulose chains from each other in the amorphous regions [23]. In a consecutive manner, the cellulose chains are gradually disentangled and move out of the network into the bulk solution [15].

The dissolution of cellulose in a solvent is governed by free energy mixing thermodynamically [28]. All negative free energy variation indicates that the mixing process will occur spontaneously. Conversely, the mixing process may result in phase separation. Hence, the molecular weight of a polymer is an important factor in dissolution. This is due to the fact that the higher the molecular weight, the lower the entropic driving force contribution to dissolve [29]. Under these conditions, the enthalpy term is critical in establishing the sign of the Gibbs free energy change. It is indeed mentioned that polymer dissolution is frequently governed by kinetics rather than thermodynamics. A desired solvent for cellulose breakdown must be able to overcome the poor entropy gain through advantageous solvent and polymer interactions from a thermodynamic perspective [12]. Therefore, the development of new solvents should focus not only on eliminating hydrogen bonding but also on reducing the hydrophobic interactions among cellulose chains.

A good solvent is a solvent that coordinates well and is strong with the polymer [27]. The intramolecular hydrogen bonding network was broken and disrupted by the solvent, which had a significant effect on the dissolution of cellulose [30]. The ability of solvents to form hydrogen bonds is crucial for the dissolution of cellulose [31]. A good solvent for cellulose dissolution is able to overcome the low entropy gain

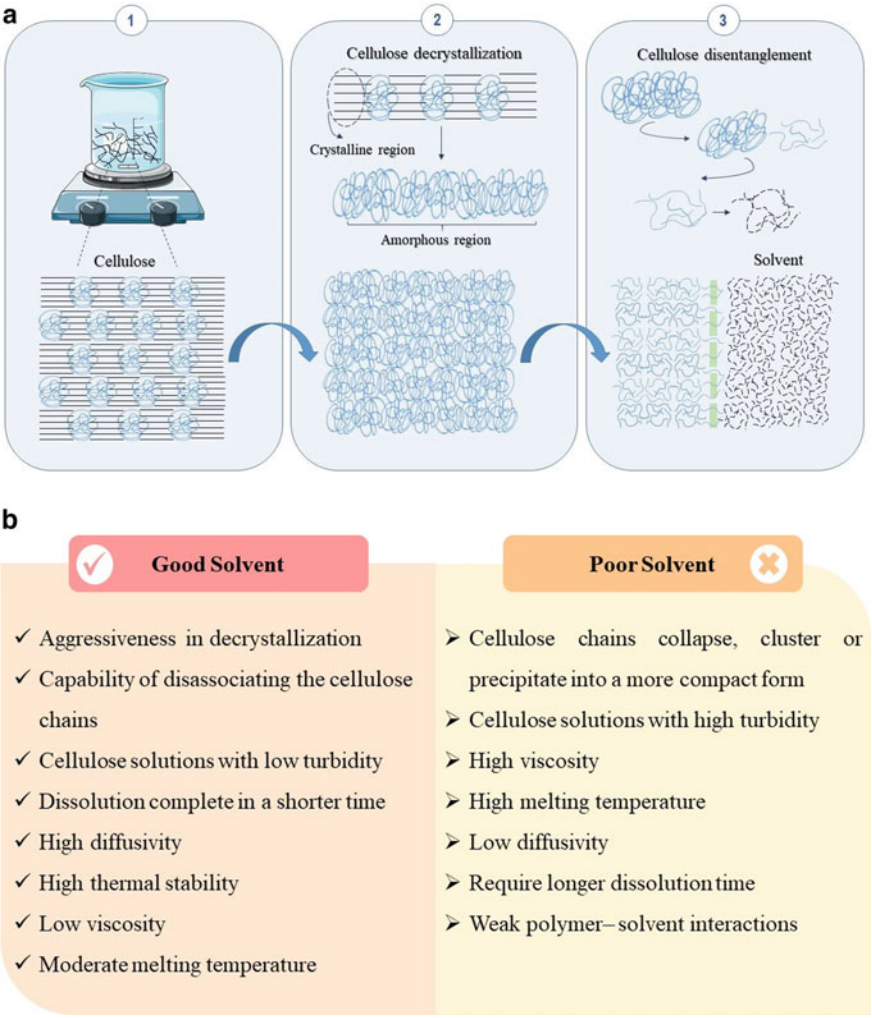


Fig. 2 **a** Schematic representation of cellulose dissolution involving the process of cellulose decrystallization and cellulose disentanglement. Stage 1: The solvent diffuses into cellulose chains, and crystalline regions are gradually break down. Stage 2: Cellulose chains disentangle from each other in the amorphous regions and move out of the network into the bulk solution, where equilibrium state is achieved. The figure (stirrer and magnetic stirrer) was partly generated using Servier Medical Art, provided by Servier, licensed under a Creative Commons Attribution 3.0 unported license". **b** Properties of the good solvent and poor solvent

by favorable solvent/polymer interactions, and better dissolution results are obtained using amphiphilic solvents that are not only able to eliminate hydrogen bonding but also eliminate hydrophobic interactions [32]. Furthermore, cellulose dissolution benefited by the solvent with lower viscosity such as deep eutectic solvent and ionic liquids [33, 34]. Low viscosity enhanced cellulose's solubility by facilitating the accessibility of the solvent to the hydrogen bonds [35, 34, 31, 32] Also, good solvents showed high solubility with the properties of high transparency and low viscosity after the cellulose dissolution and regeneration process. The increase in transparency of the cellulose solutions due to good cellulose solubility was caused by the reduction of the crystalline area.

Meanwhile, in the majority of the poor solvents, cellulose is not dissolved down to a molecular level, and the cellulose chains collapse, precipitating and clustering into a more impact form [32]. In addition, a poor solvent only has weak or almost no coordination with the polymer [27]. Poor solvent with high viscosity leads to the reduction of the intermolecular collisions as high viscosity is not conducive to the mass transfer between the cellulose and the solvent [37]. This can reduce the solubility and thus increase the turbidity of the cellulose solutions. Hence, a desirable cellulose solvent should meet the term such as high diffusivity, low viscosity, and capability to maximize the solvent-polymer interactions, high thermal stability, and moderate melting temperature as well. The characteristics of the good solvent and the poor solvent are shown in Fig. 2b.

3 Ionic Liquids and Their Physicochemical Properties

Ionic liquid (IL) chemicals the so-called 'designer chemical' can be categorized as organic-based or inorganic-based IL. Generally, IL as a form of a green solvent which comprises of anion (negative ion) and cation (positive ion). Some ionic liquids (ILs) are categorized as room temperature ionic liquid (RTIL)-based which is defined as IL being present below/under room temperature. This organic-based IL, RTIL [38], is usually more favorable in the industrial applications due to its milder technical and environmental-friendly handling characteristics [38]. They are usually composed of organic cation and combined with an inorganic or organic anion [39]. Examples of cation skeletons are observed which include imidazolium, pyridinium, pyrrolidinium, piperidinium, quaternary ammonium, sulfonium, and phosphonium-based [40] IL. It was shown by the work of [39] that there is no covalent bond between anion and cation of the IL and the weak hydrogen bonds are present.

In general, there are many kinds of IL examples for various application, for instance, phenyltrifluoborate-based $[PhBF3]^-$ anion based [40], dicationic [41] (i.e., high-temperature lubricant), carbon functionalized liquids [42], hydrophilic immidazolium based IL [43], lithium ionic liquid LiTFA [44], organoindate ionic liquid [45], tetrabutylphosphonium carboxylate [46], phosphorodithioate-functionalized ionic liquid [47], protic ionic liquid [48], imidazolium ionic liquid [49], and trialkylphosphonium-based protic IL [50]. These 'designer chemicals' of IL can

function according to the many kinds of intended tasks, for instance, for electrochemical industrial applications [40], membrane separation, or even for the pretreatment of certain lignocellulosic biomass (LCB) with the tailored anion and cation [51]. Table 1 shows some of the examples of cation and anion skeletons from the most common cation skeletons mentioned earlier with the pretreatment of LCB for cellulosic dissolution.

Table 1 indicates the lists of ionic liquid for imidazolium, pyridinium, pyrrolidinium, piperidinium, including piperazinium and quaternary ammonium based from reported cellulosic dissolution investigations as tabulated. The investigations covered wood or microcrystalline cellulose or Avicel particles for cellulose dissolution results. In overall, the acetate anions are seen to be very effective in increasing the dissolution of these IL. Besides being proven by Zavrel et al. [52] the effectiveness of [EMIM]Ac (acetate as anion), even to the hardest dissolution using pyrrolidinium, piperidinium including piperazinium and quaternary ammoniu, can now with the help of newly formulated mixture with dimethyl sulfoxide (DMSO) co-solvent, dissolution is already partially possible.

The physicochemical properties of the IL are crucial for the technical understanding of the applicability of the anion or cation roles in any industrial applications, specifically with the optimized alkyl-chain length design [38]. Most common physicochemical properties are molecular weight, melting point temperature (i.e., for solid IL), density, thermal stability, viscosity, thermal stability, and hydrophilicity/hydrophobicity. The anion effect on the melting point and viscosity relationship is significant, and it is known that the viscosity of IL is higher than the viscosity of water [51].

The determination of these physicochemical properties can be carried out using density functional theory (DFT) theoretically or by using the program of Cosmotherm [39] to correlate the viscosity and Van der Waals energy of the ionic liquid, via chromatography method [38], nuclear magnetic resonance (NMR) spectroscopy [57] (gas solubility), thermogravimetric analysis (TGA) [41, 50] (thermal decomposition temperature/thermal stability), UV-Vis spectroscopy, thermogravimetric mass spectrometric analysis (TG-MS), differential scanning calorimeter (DSC) [41, 50] (melting points), viscometer [41, 50] (viscosity), ac impedance measurement [50] (conductivity), electrospray ionization mass spectrometry (ESI-MS) [41] (molecular weight), specific gravity pycnometer [41] (density), etc. It was reported that gas chromatography method is the most favorable as compared to the conventional method determination due to few advantages besides being fast during determination and having an excellent accuracy, the sample needed to measure in gas chromatography is also very minimal [38].

The physicochemical properties change with different combinations of certain cations to variety of anions. Poole and Atapattu [38] reported the solubility parameters via gas chromatography for various ionic liquid. The solubility parameters are used to estimate the solubility of solutes of ionic liquid. When the anion was changed for instance from bromide to chloride with the same cation, the solubility parameter increased slightly, for instance, for 1- Allyl-3-methylimidazolium-based IL from 26.24 to slightly above the earlier solubility parameter, respectively. As

Table 1 Most common cation and anion skeletons for ionic liquid imidazolium, pyridinium, pyrrolidinium, piperidinium, quaternary ammonium, sulfonium, and phosphonium based from reported cellulosic dissolution investigations

Name	Abbreviation	Cation	Anion	Dissolution potential, C[a]	Dissolution potential, C[a]	References
Imidazolium-based						
1-Allyl = 3-methylimidazolium-chloride	[AMIM] Cl	[AMIM]	Cl	//, Wood	//, Avicel	[52]
1-Butyl-3-methylimidazolium-bromide	[BMIM] Br	[BMIM]	Br	–	/, Avicel	
1-Butyl-3-methylimidazolium-chloride	[BMIM] Cl	[BMIM]	Cl	/, Wood	//, Avicel	
1-Butyl-3-methylimidazolium-hexafluorophosphate	[BMIM]PF_6	[BMIM]	PF_6	–	X	
1-Butyl-3-methylimidazolium-iodide	[BMIM] I	[BMIM]	I	–	/, Avicel	
1-Butyl-3-methylimidazolium-methanesulfonate	[BMIM] CH_3SO_3	[BMIM]	CH_3SO_3	–	X	
1-Butyl-3-methylimidazolium-tetrafluoroborate	[BMIM]BF_4	[BMIM]	BF_4	–	X	
1-(2-Hydroxylethyl)-3-methylimidazolium-tetrafluoroborate	[HEMIM]BF_4	[HEMIM]	BF_4	–	X	
1-Ethyl-3-methylimidazolium-acetate	[EMIM]Ac	[EMIM]	Ac	//, Wood	//, Avicel	
1-Ethyl-3-methylimidazolium-bis(trifluoromethylsulfonyl)imide	[EMIM]BTI	[EMIM]	BTI	–	X	
1-Ethyl-3-methylimidazolium-chloride	[EMIM]Cl	[EMIM]	Cl	/, Wood	//, Avicel	
1-Ethyl-3-methylimidazolium-ethylsulfate	[EMIM] $C_2H_5OSO_3$	[EMIM]	$C_2H_5OSO_3$	–	X	
1-Ethyl-3-methylimidazolium-tetrafluoroborate	[EMIM]BF_4	[EMIM]	BF_4	–	X	
1-Hexyl-3-methylimidazolium-chloride	[HMIM] Cl	[HMIM]	Cl	–	/, Avicel	
1-Hexyl-3-methylimidazolium-tetrafluoroborate	[HMIM]BF_4	[HMIM]	BF_4	–	X	
1-Methyl-3-octylimidazolium-chloride	[OMIM] Cl	[OMIM]	Cl	–	X	
1,3-Dimethylimidazolium-dimethylphosphate	ECOENG	[ECOENG]	Dimethylphosphate	/, Wood	//, Avicel	

(continued)

Table 1 (continued)

Name	Abbreviation	Cation	Anion	Dissolution potential, C[a]	Dissolution potential, C[a]	References
Pyridinium-based						
1-Butyl-3-methylpyridinium-chloride	[BMPY]Cl	[BMPY]	Cl	–	/, Avicel	[52]
Pyrrolidinium-based						
N-Butyl-*N*-methylpyrrolidinium	[C4mpyr][OH]	[C4mpyr]	[OH]	–	/, Avicel	[53]
N-ethyl-*N*-methylpyrrolidinium acetate	([EMPyrr][Ac])/DMSO	([EMPyrr] with DMSO solvent)	[Ac]	–	/, MCC	[54]
Piperidinium-based or piperazinium-based						
Poly(ethylene glycol) PEG-functionalized piperidinium-based	[Me(OCH_2CH_2)3-Et-Pip][OAc]	[Me(OCH_2CH_2)3-Et-Pip]	[OAc]	–	/, Avicel	[55]
N,*N*'-Dimethyl-*N*-ethylpiperazinium acetate	[DMEPpz][Ac]/DMSO)	[DMEPpz][with DMSO solvent	[Ac]	–	/, MCC	[54]
Quaternary ammonium-based						
Tetra(n-butyl)ammonium acetate	NBu_4AcO	NBu_4	AcO	–	/, Avicel	[56]
Diallyl-benzyl-methylammonium (AlAllyl)	NAl2BzMe AcO	NAl2BzMe	AcO	–	/, Avicel	

C = type of cellulosic matter investigated

[a] Defined as at 40–50 °C operating temperature high throughput screening; / = partial dissolution; // complete dissolution; X = no dissolution; MCC = microcrystalline cellulose

for 1-Butyl-3-methylimidazolium as IL cation, when the anion changed from like hydrogen sulfate, perchlorate, methyl sulfate, thiocyanate, and octyl sulfate, causing the solubility parameter to change/differ to be in the range of between 23 and 27. Another example of the change of the solubility parameter happens on 1-Ethyl-3-methylimidazolium as IL cation, changed from 23.2 to 25.56 for the use of anion of acetate and trifluoroacetate, respectively.

Table 2 below shows the exemplary physicochemical properties of various ionic liquids as previously reported able to dissolve cellulose completely by Zavrel etal. [52]. The exemplaries were taken from Sigma Aldrich Safety Data Sheet (SDS) indicating molecular weight, melting point, density, flash point, melting point, and pH. The melting point temperature of lower or close to the ambient temperature or pressure, resulting in the IL to be in the liquid form. Vice versa, if the melting point is higher than the ambient, either crystal solid or solid particles are formed like 1-Allyl-3-methylimidazolium chloride [AMIM]Cl and 1-Butyl-4-methylpyridium chloride [BMPY]CL (refer to Table 2).

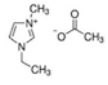
3.1 Role of Ionic Liquid in Cellulose Dissolution

In this case, the cellulose and hemicellulose matters are partly comprised in the lignocellulosic biomass (LCB), the biopolymer source [58]. The biopolymer itself which contains polysaccharides, is regarded as mainly containing the cellulosic matter in majority percentage of the LCB besides the noncellulosic matter which is lignin. The cellulosic matter (cellulose or hemicellulose) dissolution is one of the methods used to separate the cellulose compounds from the LCB, knowing the fact that the biopolymer which contains the cellulose, hemicellulose, and lignin, is being strongly bonded by the carbon-hydrogen structures or by the strong intermolecular interactions within the biopolymer.

The pretreatment of the LCB is the most crucial step particularly to support the sustainability green energy-efficient method and the overall cost incurred due to the pretreatment of the LCB. Cellulose is not easily dissolved in water due to the highly organized cellulose chain structure (highly crystalline) [58]. The known internal bonds present in LCB which are ®-(1,4)-glycosidic bond, ®-(1,3)-glycosidic bond, hydrogen bond, aryl-ether bond, and C–C bond, contribute to the recalcitrance of dissolution of LCB [58]. These bonds can be broken with various methods, for instance, with strong acidic or alkaline solution at certain temperature and pressure as the so-called chemical or physicochemical methods, for instance, besides the ionic liquid pretreatment method.

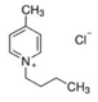
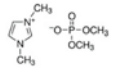
Ionic liquid assisted dissolution method is already known to be one of the pretreatment methods used, using ionic liquid with certain characteristics of the anions and cations and able to dissolve cellulosic matter either from wood chip or fibrous plant, as indicated by Fig. 3a. In order to obtain the cellulosic biomass from liquid to solid, after the pretreatment step, certain anti-solvents are mixed (as quenching) to the pretreated solution (containing dissolved cellulose) at ambient temperature for

Table 2 Exemplary physicochemical properties of various ionic liquids as reported able to dissolve cellulose completely[a]

Name	Form	Empirical formula	Structure	Molecular weight [g/mol]	Density [g/cm^3] at 25 °C	Flash point [^{o}C]	Viscosity	Color	Melting point [^{o}C]	pH	HB/HF	Brand/References
Aprotic room temperature ionic liquid RTIL												
1-Ethyl-3-methylimidazolium acetate 96.5% (HPLC)	Liquid	$C_8H_{14}N_2O_2$ [EMIM]Ac		170.21	1.027	164	NDA	NDA	>30	5.4 at 100 g/L	HP	Sigma Aldrich
Thermostable and task-specific ionic liquid (TSIL)												
1-Allyl-3-methylimidazolium-chloride ε 97.0% (HPLC)	Crystal	$C_7H_{11}ClN_2$ [AMIM]Cl		158.63	NDA	NA	NDA	Light orange	NDA, 35 °C	NDA	HP	Sigma Aldrich
Organoaluminate molten salt												
1-Butyl-3-methylimidazolium chloride ε 98.0% (HPLC)	Solid	$C_8H_{15}ClN_2$ [BMIM]Cl		174.67	1.086 (at 20 °C)	192	NDA	Light yellow	70	7.9 at 100 g/L	HB	Sigma Aldrich
Organic salt and RTIL, organic reaction solvent, small vapor pressure, high thermal stabilities, ionic conductivity												
1-Ethyl-3-methylimidazoliu chloride ε 98.0%	Solid	$C_6H_{11}ClN_2$ [EMIM]Cl		146.62	1.189 (at 20 °C)	188	NDA	Beige	77–79	NDA	HP	Sigma Aldrich

(continued)

Table 2 (continued)

Name	Form	Empirical formula	Structure	Molecular weight [g/mol]	Density [g/cm^3] at 25 °C	Flash point [^{o}C]	Viscosity	Color	Melting point [^{o}C]	pH	HB/HF	Brand/References
Other												
1-Butyl-4-methylpyridinium-chloride ε 97.0%	Crystal	$C_{10}H_{16}ClN$ [BMPY]Cl		185.69	NDA	NDA	NDA	Light brown	158–160	NDA	HB	Sigma Aldrich
1,3-Dimethylimidazoliu m dimethyl phosphate ε 98.0%	Liquid	$C_7H_{15}N_2O_4P$ ECOENG		222.18	1.277 (at 20 °C)	NDA	NDA	Yellow	NDA	2.4 at 20 °C	–	Sigma Aldrich

[a] NA = non applicable, NDA = No data available, HB = hydrophobic, HP = hydrophilic

instance by using water, ethanol, or acetone. This is called as regeneration of dissolved cellulosic matter after pretreatment step. In a recent study, ethanol was applied as non- solvent to regenerate rice straw cellulose-based hydrogel via phase inversion method [57]. Highly disordered structures as observed via X-ray diffraction analysis (for the 2 readings versus intensity) indicate lower crystalline with higher amorphous regions [60]. These anti-solvents which are considered as non-toxicity chemicals, not as much as some other organic co-solvent like dimethylformamide (DMF), dimethyl sulfoxide (DMSO), or dimethylacetamide (DMAc). In some reports, it was reported that the ionic liquid-cosolvent combinations are becoming also effective with the recent report (see below).

The ionic liquid's role is mainly to disrupt the crystalline structure of cellulose, thus reducing the crystallinity of the cellulosic matter mainly the cellulosic matter [61]. Cellulose itself is bonded to oxygen-hydrogen atoms (OH) and during the dissolution, the strong bond of hydrogen to others is the key to dissolution. The interactions between oxygen and hydrogen atoms of the cellulose-OH together with the anions and cations from ionic liquid break the intended bond holding the cellulose and hemicellulose within lignin in LCB within the molecular chains of cellulose in LCB. It was reported that cations (positive ions) interacted with hydroxyl oxygen atom present in the cellulosic bond of the cellulosic matter.

Figure 3b shows the effect of the cation and anion examples from 1-Ethyl-3-methylimidazolium acetate [EMIM]Ac on the OH bonds in cellulose and hemicellulose. The green and red boxes refer to cation and anion from [EMIM]Ac, respectively, which then influence the attack on respective OH bonds in cellulose and hemicellulose (as shown by the color coding boxes), in addition to the influence of the physicochemical parameters of the operating steps, for instance, temperature, power input via shaking frequency (for mixing/agitation mode), particle size (surface area), and solid loading (solid to liquid ratio) during the pretreatment. For some other ILs other than [EMIM]Ac, the possibility of bond breakage in lignin by cation and anion is also possible (not shown here).

Ionic liquid which was earlier mentioned to be capable to dissolve the cellulosic matter, the 1-ethyl-3-methylimidazolium acetate [EMIM]Ac was concluded by the major comprehensive investigations. Verma et al. [51] and Zavrel et al. [52] have already started the investigations, for instance, via the high-throughput screening of the possible ionic liquids, in ensuring the green solvent method application by Verma et al. [51] and Zavrel et al. [52], since 2009, comprising of imidazolium, pyridinium, and butyl phosphonium chloride of two different states of solid and liquid. The study found out that EMIMAc from the imidazolium based was the most effective IL during the dissolution of cellulosic matter. Figure 3a below shows the dissolution of lignocellulosic matter in ionic liquid overview from lignocellulosic biomass feedstock being introduced to various ionic liquid types which are capable to dissolve the cellulosic content producing liquid sample containing dissolve cellulose prior to the regeneration of cellulose using antisolvent solution. It indicates the solid LCB was in total dissolution with pure ionic liquid.

As mentioned in the earlier section, the physicochemical properties of the ionic liquid are crucial in this case for the designed role of the cation and anion, in the sense

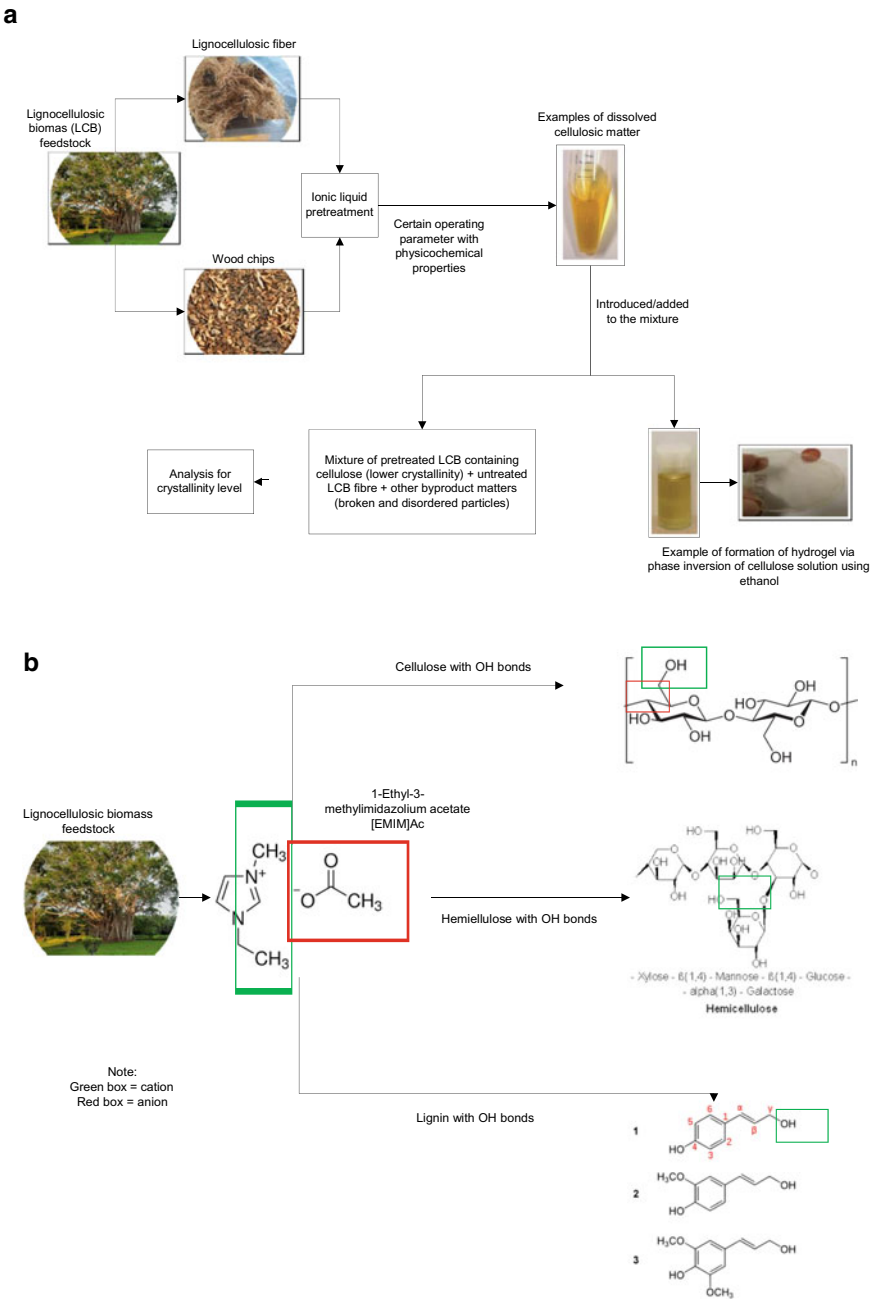


Fig. 3 **a** Dissolution of lignocellulosic biomass direct simple overview in pure ionic liquid example of the pretreatment step. **b** Ionic liquid cellulose dissolution influence on the oxygen-hydrogen bonds example by 1-ethyl-3-methylimidazolium acetate [EMIM]Ac on lignocellulosic biomass feedstock via cation and anion effect

of viscosity and thermal stability via melting point. High viscosity of the ionic liquid during pretreatment may disrupt the liquid-solid handling of the pretreatment process conditions. The rule of thumb is to have less viscous solvent solution, and the high capability to dissolve LCB at ambient temperature for balanced techno-economic feasibility of the pretreatment process itself.

Ionic liquids which have been reported to dissolve the cellulosic matter partially or completely as earlier introduced in Table 1 and 2 as in the introductory section, have supported the pretreatment of LCB theme using green solvent, the IL.

Latest findings recently reported on mixed co-solvents which showed better dissolution for some of the IL types. Kasprzak et al. [54] reported 13.5 wt% of cellulose dissolution with *N*,*N*'-dimethyl-*N*-ethylpiperazinium acetate ([DMEPpz][Ac]/DMSO) mixed solvent at the temperature of 80 °C via microcrystalline cellulose as the representative of cellulosic matter. *N*-Ethyl-*N*-methylpyrrolidinium acetate ([EMPyrr][Ac])/DMSO was as also reported by Kasprzak et al. [54], indicated slightly lower wt% of cellulose dissolution of only 9.5 wt% cellulose solubility at the same temperature as ([DMEPpz][Ac]/DMSO) cellulose pretreatment. For the quarternary ammonium-based IL as tabulated in Table 1 earlier, approximately of 10–12 wt% of reached dissolved cellulose were successfully reported with DMSO co-solvent during the cellulose dissolution experiments of electrolyte-IL test [56].

3.2 Benefits and Drawbacks of Ionic Liquid

Ionic liquid can be vastly useful in agriculture, medicine, and bioprocessing aspect as reported by Flieger and Flieger [62]. However, in relationship to the cellulose application particularly the cellulosic matter dissolution with ionic liquid, there are some benefits and drawbacks of it. The ionic liquid being claimed as green solvent initiates the technological operating parameters at not extreme conditions relating to temperature and pressure (ambient or close to ambient) and concentration of the ionic liquid (mild to pure) which may not be as much corrosive as alkaline or acidic pretreatment solvents. Some ionic liquids have been also developed to behave as inhibitor to corrosion, seen to be promising, green, and sustainable [63].

The most challenging, in one perspective, is not the toxicity of ionic liquid used but the techno-economic feasibility of the chemicals used during the pretreatment of LCB itself due to the current highly expensive cost of certain effective ionic liquids. Thus, recycling IL for reuse is highly recommended. On the other hand, for any chemicals, if are not contained or treated well prior to disposal, the effect of exposure of the ionic liquid can be disastrous to any aquatic organisms.

Other than that, the ionic liquid itself is easy for recycling (product recovery), for instance, by evaporating the ethanol solvent and to use centrifugation to separate lignin out of the ionic liquid solid-liquid mixture solution [64, 65]. The separated ionic liquid can be recycled for reuse in the pretreatment process for more than once.

4 DESs and Their Physicochemical Properties

DESs were reported by Abbott et al. [66] for the very first time. DESs are systems formed from a eutectic mixture of Lewis or Bronsted acid and bases that contain a variety of anionic and cationic species [67]. In contrast, a mixture of chemical compounds known as a eutectic system demonstrates a single chemical composition that freezes at lower temperatures than any other composition [68]. In addition, ionic liquids were typically generated by systems containing only single type of distinct anion and cation [69]. Generally, two or more components are mixed together at a specific temperature to develop the eutectic mixture [68]. DESs are procured from the complexation of a quaternary ammonium salt with a metal salt or hydrogen bond donor through hydrogen bonding [67]. The terms "hydrogen bond acceptor" (HBA) and "hydrogen bond donor" (HBD) relate to the acceptance and donation of protons, respectively. Components such as Cl^-, $(MeO)2PO^{2-}$, $HCOO^-$, OAc^-, imidazole, as well as morpholine, which have strong hydrogen bond accepting ability, have been identified as possible choices for forming DESs [70]. The structure and various varieties of HBA and HBD, which are commonly used to produce DESs, are shown in Table 3.

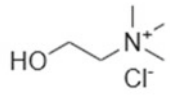
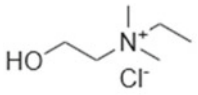
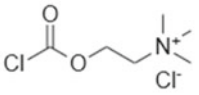
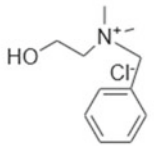
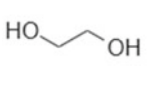
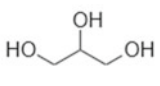
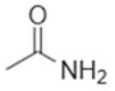
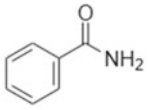
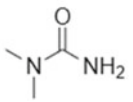
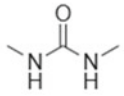
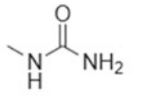
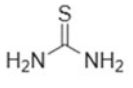
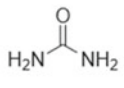
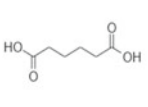
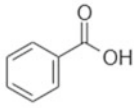
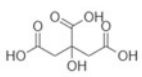
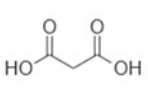
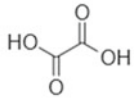
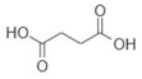
In general, there are various types of DESs which are applied in many industries. The mixtures exhibited amphiphilic behavior and could be used in a liquid state [71]. Additionally, the melting point of DESs is substantially lower than the relevant values of the individual mixture component values. [72]. They also exhibit non flammability, low vapor pressure, and a relatively wide liquid range [69]. Vigier et al. [73] elucidate that the distinctive structures of the HBA and HBD contribute to the dissolution of cellulose biomass. Hence, Chen et al. [67] mentioned that DESs have analogous physico-chemical properties to ionic liquids, and they are anticipated to be used as an alternative solvent to dissolve the cellulose due to their analogous physico-chemical properties to ionic liquids. Moreover, different combinations and selections of the constituents nature and ratio can result in different physiochemical properties [67]. The most common physiochemical properties are freezing point, viscosity, conductivity, pH, density, polarity, acidity, or alkalinity [12].

4.1 Role of DESs in Cellulose Dissolution

Recently, efforts have been undertaken to dissolve cellulose in DESs. In the study by Zhang et al. [74], an eutectic mixture made up of tributylmethylammonium chloride ($[N_{4441}]Cl$) and cholinium acetate ($[Ch][CH_3COO]$) showed the ability to dissolve the cellulose up to 6 wt%. The results are similar to the results obtained using a number of ILs, making this eutectic mixture a great way to develop a novel DESs that can dissolve cellulose.

At present, choline chloride (ChCl) is one of the HBA which is most frequently used as it can combine with other safe and inexpensive HBD like urea, glycerol,

Table 3 Typical structures of the halide salt and hydrogen bond donor for the formation of deep eutectic solvents

Hydrogen bond acceptors		
1	Choline chloride	 1
2	*N*-Ethyl-2-hydroxy-*N*,*N* -dimethylethananium chloride	 2
3	2-(Chlorocarbonylox)-*N*,*N*,*N*-trimethylethanaminium chloride	 3
4	*N*-Benzyl-2-hydroxy-*N*,*N*-dimethylethanaminium	 4
Hydrogen bond donors		
1	Ethylene glycol	 1
2	Glycerol	 2
3	Acetamide	 3
4	Benzamide	 4
5	1,1-Dimethyl urea	 5
6	1,3-Dimethyl urea	 6
7	1-Methyl urea	 7
8	Thiourea	 8
9	Urea	 9
		 10
		 11
		 12
		 13
		 14
		 15

(continued)

Table 3 (continued)

Hydrogen bond acceptors		
10	Adipic acid	
11	Benzoic acid	
12	Citric acid	
13	Malonic acid	
14	Oxalic acid	
15	Succinic acid	

imidazole, and shuttle acid to form DESs [37]. As a result, the cellulose dissolution started with the ChCl-based DESs [67]. The anion and cation play important roles in cellulose breakdown in ionic liquids by creating hydrogen bonds with the hydroxyl protons of cellulose [75, 76]. Ren et al. [33, 34] concluded similar findings where the protic –OH groups in ChCl-based DESs showed the ability to react with cellulose. ChCl solvent formed new hydrogen bonds with the hydroxyl groups of the cellulose through its oxygen atom in the hydroxyl group and its nitrogen atom in the amino group. Also, DESs did not weaken the interactions between anions and cations in hydrogen bonds in cellulose but did compete with the cellulose hydrogen bonds. After the deep eutectic melt formed an internal hydrogen bond, a large number of remaining ions formed a hydrogen bond with the hydroxyl groups of the cellulose, which became strong and the solubility of the cellulose became high [37].

Zhou and Liu [77] tested the dissolution of cotton linter pulp in a novel DErrSs by using ChCl and caprolactam. The cotton linter pulp was found to be soluble at 120 °C with a solublity of 0.16 wt%. Ren et al. [33, 34], further studied four types of DESs based on ChCl and urea, imidazole, ammonium thiocyanate, and acetamide, respectively, for cellulose dissolution. The cellulose was activated by employing saturated calcium chloride solution with ultrasound assistance in order to increase the cellulose dissolution. ChCl-Imidazole DESs with the highest Hammett acidity function, dipolarity/polarizability effect, and hydrogen bond basicity exhibited the highest solubility of cellulose (2.48 wt%). Malaeke et al. [78] recently investigated the cellulose dissolution efficiency of a series of DESs based on choline chloride, phenol, naphthol, resorcinol, and maleic acid. The best effects in terms of solubility were showed in choline chloride and resorcinol with a 6.10 wt%. These findings reported that the cellulose can be dissolved by the DESs by using ultrasound irradiation.

Zhang et al. [37] examined the properties of ChCl/urea, ChCl/citric acid, ChCl/oxalic acid, and ChCl/glycerol on cellulose dissolution. The ChCl/oxalic acid exhibited the best dissolution effects on cellulose with 2.54 wt% at 100 °C. Francisco et al. [79] investigated 21 different DES varieties with various molar ratios to discover additional DESs for the dissolution of cellulose. The DESs composed of malic acid and proline were reported to have the highest solubility of the cellulose (0.78 wt%) at 100 °C. Meanwhile, Zhou and Liu [77] used caprolacram and urea in a 1:3 molar ratio to achieve maximum solubility of 2.83 wt% at 50 °C. Despite the low cellulose solubility in these DESs, Ren et al. [33, 34], synthesized

a new allyl-functionalized choline DESs to promote cellulose dissolution. Triethyl-allyl ammonia chloride/oxalic acid was reported to have the highest solubility of cellulose at 6.48 wt%.

Choline and L-Lysine hydrochloride DESs were employed in the study by Wang et al. [70], to dissolve the cellulose isolated from wheat straw, and the results indicated outstanding stability with the greatest solubility of 5 wt%. Components of lignocellulosic biomass, such as cellulose, were examined for dissolution in DESs by Lynam et al. [80]. The maximum cellulose solubility was achieved at around 3 wt% with ChCl-lactic acid DESs with a molar ratio of 1:10. Besides, the solvent had been used to delignify cellulose, leaving the structure intact. Mamilla et al. [81] recently showed that DESs comprised of ChCl and KOH may selectively dissolve cellulose from biomass while leaving a solid residue rich in lignin. The DESs that are currently reported to be solvents for cellulose dissolving are listed in Table 4.

Chen et al. [67] revealed that the insolubility or low solubility of cellulose in DESs is due to the strong intermolecular hydrogen interactions between cellulose molecules and the breaking of hydrogen bonds is required to transform cellulose into solution. According to Lindman et al. [15], low aqueous solubility of the cellulose cannot be explained by the hydrogen bonding theory. It has been suggested that hydrophobic interaction and co-solvents can play a significant role in cellulose's low aqueous solubility. Latest findings recently reported that mixing of co-solvents showed better

Table 4 Solubility of cellulose in DESs

Cellulose type	DESs	Molar ratio	Condition	Solubility (wt%)	References
Cotton linter pulp	ChCl/urea	1:2	Activating cellulose by ultrasound assisted saturated calcium chloride solution prior dissolution; processing at 120 °C	1.43	[33, 34]
	ChCl/imidazole	3:7		2.48	
	ChCl/ammonium thiocyanate	1:1		0.50	
	ChCl/acetamide	1:2		0.22	
Microcrystalline cellulose AVICEL PH 105	ChCl/urea	1:2	Dissolution at 110 °C	<0.2	[74]
	ChCl/$ZnCl_2$	1:2		<0.2	
Cellulose (≥98% mass fraction purity)	ChCl/maleic acid	1:1	Processing with ultrasonic irradiation (20 Hz) at 90 °C	2.57	[78]
	ChCl/α-naphthol	1:1		3.39	

(continued)

Table 4 (continued)

Cellulose type	DESs	Molar ratio	Condition	Solubility (wt%)	References
	ChCl/phenol	2:1		4.70	
	ChCl/resorcinol	1:1		6.10	
Cotton linter pulp (DP = 575.6)	ChCl/caprolactam	1:1	Activating cellulose by ultrasound assisted saturated calcium chloride solution prior dissolution; dissolution at 120 °C	0.16	[77]
Cotton ramie pulp (DP = 517)	Acetamide/caprodacine	1:1	Dissolution at 50 °C	1.79	[77]
	Acetamide/urea	2:1		1.03	
	Caprolactum/urea	3:1		2.83	
Microcrystalline cellulose	ChCl/urea	1:2	Dissolution at 100 °C	1.03	[37]
	ChCl/citric acid	1:2		1.94	
	ChCl/oxalic acid	1:2		2.54	
	ChCl/glycerol	1:2		0.6	
Cellulose extracted from wheat straw	Choline/L-lysine hydrochloride	2:1	Processing with ultrasonic grinding (600 W) at room temperature; dissolution at 90 °C	5.0	[70]
Medium fibrous cellulose	ChCl/lactic acid	1:10	Dissolution at 60 °C	3.0	[80]
Cellulose (≥90% mass fraction purity)	Malic acid/alanine	1:1	Dissolution at 100 °C	0.11	[79]
	Malic acid/glycine	1:1		0.14	
	Malic acid/proline	1:2		0.24	
	Malic acid/proline	1:3		0.78	
	Oxalic acid dihydrate/histidine	9:1	Dissolution at 60 °C	0.25	

cellulose dissolution for DESs comprised of choline chloride and imidazole. Ren et al. [33, 34] reported that 4.57 wt% of cellulose is dissolved in the ChCl-Imidazole DESs coupled with polyethelyne glycol (PEG) at a temperature of 100 °C. In this example, PEG was used as a surfactant to minimize the hydrophobicity of cellulose and hence increase the permeability of DES. This enables a more effective interaction with DESs

components through hydrogen bonding with the hydroxyl group or hydrophilic part of PEG. As a result, cellulose became more hydrophilic with the addition of PEG [33].

As mentioned in the earlier section, the permeability and interactions between cellulose and solvent are critical toward the solubility of cellulose. Therefore, the hydrogen bond accepting ability of DESs must be increased. In order to estimate the ability of the solvent, the Kamlet-Taft parameter is a useful tool to specify three distinct solvent polarities, including the hydrogen bonding acidity (α), hydrogen bonding basicity (β), and dipolarity/polarizability (π*) [82]. The result shows that the stronger the hydrogen bond acceptance of the DESs, the stronger the ability of the DESs to dissolve the cellulose [33, 34]. The inter- and intramolecular hydrogen bonds in the cellulose crystals can be weakened by the high hydrogen bonding basicity; therefore, the β values can be a trustworthy indicator of the capacity to dissolve cellulose. In addition, analysis such as NMR, FTIR, and theoretical calculations can be performed to further explore the interactions between the solvent agents and cellulose. Recently, the authors determined that when cellulose is dissolved in DESs, the H bonds in the DESs weaken because the HBA and HBD form non-covalent interactions with cellulose. On the other hand, this breaks down the H bonds within and between cellulose chains, loosening the structure and causing disintegration [83].

ILs have been shown to be more effective than DESs at dissolving cellulose globally. Häkkinen and Abbott [84] recently discussed the distinctions between ILs and DESs in terms of cellulose dissolution. The greater solubility of cellulose in some ILs was linked to their innate highly ordered structure, which suffers a degree of chaos when in contact with cellulose, allowing for an entropy gain. The lower-order conformation of the DES, on the other hand, prevents this entropy gain, resulting in limited or non-existent cellulose solubility. In conclusion, more research and development should be conducted to prove novel DESs that can dissolve cellulose.

4.2 Benefits and Drawbacks of DESs

DESs have a number of advantages over conventional ILs, including ease of preparation and availability from relatively low-cost components and being less chemically inert [69]. Furthermore, according to [85], DESs have attractive properties like biodegradability, low cost, low volatility, non-toxicity, and ease of preparation. In general, the two components are simply mixed together and then heated to a moderate temperature to create DESs. Therefore, this allows for large scale applications while maintaining a low production cost compared to conventional ILs. DESs can also be generated naturally, particularly from primary metabolites such as organic acids, amino acids, and carbohydrates [86, 87]. A key tool for regulating the physical properties of DESs is the wide range of potential starting materials. Therefore, DESs can replace or enhance ILs in many applications due to their similar physiochemical properties [88].

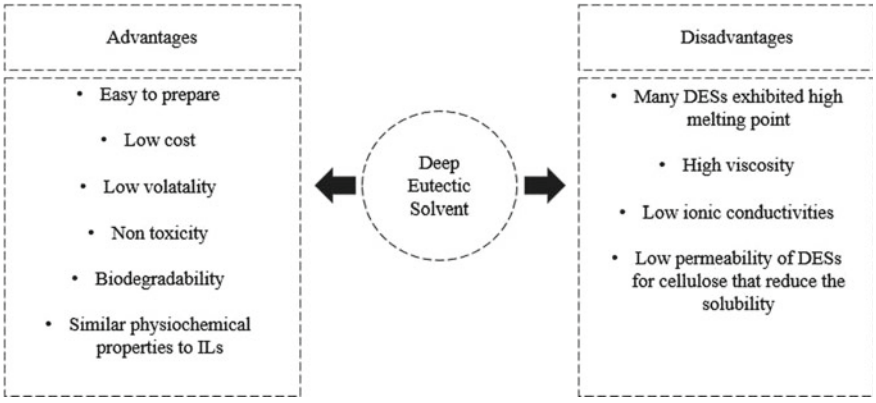


Fig. 4 Advantages and disadvantages of DESs

However, many DESs with high melting points can limit their application as green solvents when used at ambient temperature [87]. Additionally, DESs have much higher viscosities than typical small-molecule solvents [89]. Also, the high viscosity restricted the mobility of the ionic species, hence they exhibited low ionic conductivity. Chen et al. [67] revealed that DESs are not ideal solvents for cellulose dissolution. The results also showed that there were not many interactions between the solvent agents and the cellulose in the DESs' hydrogen bond network. Therefore, the permeability of DESs for cellulose is limited and causes a decline in solubility. The advantages and drawbacks of the deep eutectic solvents are listed in Fig. 4.

5 Conclusion and Perspective

Cellulose is a natural biopolymer that is made mainly of plant fibers. It is abundance everywhere, and in the recent advancements, many reckons cellulose has a shown a significant promise as the main resources for the production of sustainable and economically viable polymeric products. Indeed, a 'green' substitute to synthetic polymer-based commodity products. Nevertheless, chemical processing of cellulose is not so straight forward. This is primarily because of the complexity of the cellulose bio-polymeric network, its partially crystalline structure, and the extensive noncovalent interactions within its molecules. Clearly, in order to further modify and/or degrade such cellulose structure, a suitable solvent with the capacity to perturb the intermolecular hydrogen bonding between cellulose molecules must be applied and therefore, causing the dissolution of the cellulose biopolymer. Moreover, a desirable cellulose solvent should also feature characteristics such as low toxicity, mild melting temperature, easy handling and recycling, water-like viscosity, and excellent thermal

stability or in a general term; a 'green' cellulose solvent. In this review, our focusses were on ionic liquids (ILs) and the deep eutectic solvents (DESs) as potential green solvents for dissolution and regeneration of cellulose. Input on the properties of both solvents were presented in details in which we believed are critically important for designing green approach in dissolution of cellulose biopolymer. Also presented, are the discussion on the suitable dissolution mechanism and the effectiveness of cellulose dissolution, i.e., based on the solvents advantages and limitations – by both ILS and DESs.

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Recent Advances in Regenerated Cellulosic Materials and Composites for Multifunctional Applications: A Review

Maitry Bhattacharjee, Avik Dhar, and Partha Sikdar

Abstract Due to sustainable development policies and global concern about minimizing environmental impact, it has become a dire need to supplant petrochemical-based materials with ecologically friendly components derived from renewable resources. Consequently, cellulose has received immense research attention in recent years as one of the most abundant natural linear polysaccharide polymers due to its high biodegradability, wide availability, low costs, and biocompatibility. The appealing aspect of cellulose polymer is its inter- and intramolecular hydrogen bonding between the polymer chain's structure, which escalates its mechanical properties and makes it insoluble in common solvents. Despite this, the chain structure can be destroyed and rearranged via environment-friendly processes (physical dissolution) to construct regenerated cellulose (RC) in a variety of pure and composite forms, including nanoparticles, fibers and filaments, films/membranes, sheets, microspheres/beads, gels, microstructures/nanofibrils, and bioplastic, with divergent functions and properties. Hence, this chapter discusses the recent developments of regenerated cellulosic materials with their application in polymer and material science. The methodology of material processing, process parameters, the resultant properties, and functions are also covered in this chapter, focused on the neat regenerated cellulosic materials and their composites. Finally, the concluding section highlighted the research gap and domains where further research endeavors can be directed.

Keywords Cellulose regeneration · Regenerated cellulosic materials and composites · Structure, and properties

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1 Introduction

The ongoing demand for functional materials is being driven by population growth and industrialization. Thanks to petrochemicals, petroleum-based synthetic polymers have been widely used for a variety of applications over the last half-century, whether for industrial or household purposes. These synthetic polymers, often known as plastics, have succeeded commercially due to their light weight, good mechanical handling, low cost, and durability [1, 2]. Grievously, its discharged debris cannot be biodegraded and takes hundreds of years, even more, to break down, resulting in severe pollution worldwide [2]. It has been reported that eight million tons of plastic are discarded at sea yearly, and with the continuation of this trend, it is indisputable to find more plastic in the oceans than fish by 2050 [3]. Therefore, global pollution due to hazardous plastic waste needs to be solved urgently [4]. In addition to thinking about the way of tackling this challenge for future generations, we must ask ourselves: How can we change, or better, how can we find an impactful alternative to it? Satisfyingly, the sustainable development of chemical science is outlined through 12 principles of green chemistry which have changed the mindset of scientists [2].

Furthermore, the anticipated depletion of fossil supplies and the significant impact of nonbiodegradable materials on the environment and human health are primary motivators to employ abundant, sustainable resources. Thus, developing materials based on water, carbon dioxide, and biomass is now of critical importance. Biomass is a byproduct of plant, water, and carbon dioxide consisting of cellulose (glucose units), hemicellulose, and lignin. Every plant, natural bioresource, and biowaste has these primary components, albeit in varying quantities. In addition, many microbes get their nourishment from cellulose. Fungi and bacteria can cause cellulose chain breakdown via enzymatic or radical mechanisms [2, 5].

Cellulose, the most abundant renewable natural polysaccharide, is a linear chain comprising two anhydroglucose rings $(C_6H_{10}O_5)_n$, linked together through oxygen covalently bonded to C_1 of one glucose ring and C_4 of the adjoining ring (1–4 linkage), with the so called the 1–4 glucosidic bond (Fig. 1a). These glucoside bonds provide a flat ribbon-like conformation. The number of repeat units (n) per chain depends on the source [6–8]. It is one of the most promising substitutes for petroleum-derived synthetic polymers. Natural cellulose is the cellulose I allomorph and comes from wood, plants, tunicate, algae, bacteria, and fabric reuse and recycling to minimize the cellulose gap [9, 10]. Because of its commendable biodegradability and biocompatibility, cellulose, its modifications, and derivatives are widely used in a broad array of applications such as textile, furniture, clothing, packaging, paper, separation, electronics, and medical products in our daily life as biobased materials, such as fibers, films, food casings, and membranes [11, 12]. The majority of these applications contain a semicrystalline form of cellulose (cellulose II), known as regenerated cellulose (RC) which is the most thermodynamically stable modification [2]. The extreme difficulty of dissolution, on the other hand, is one of the most difficult challenges in the chemical processing of cellulose. In general, cellulose does not melt due to degradation before melting. It is insoluble in common

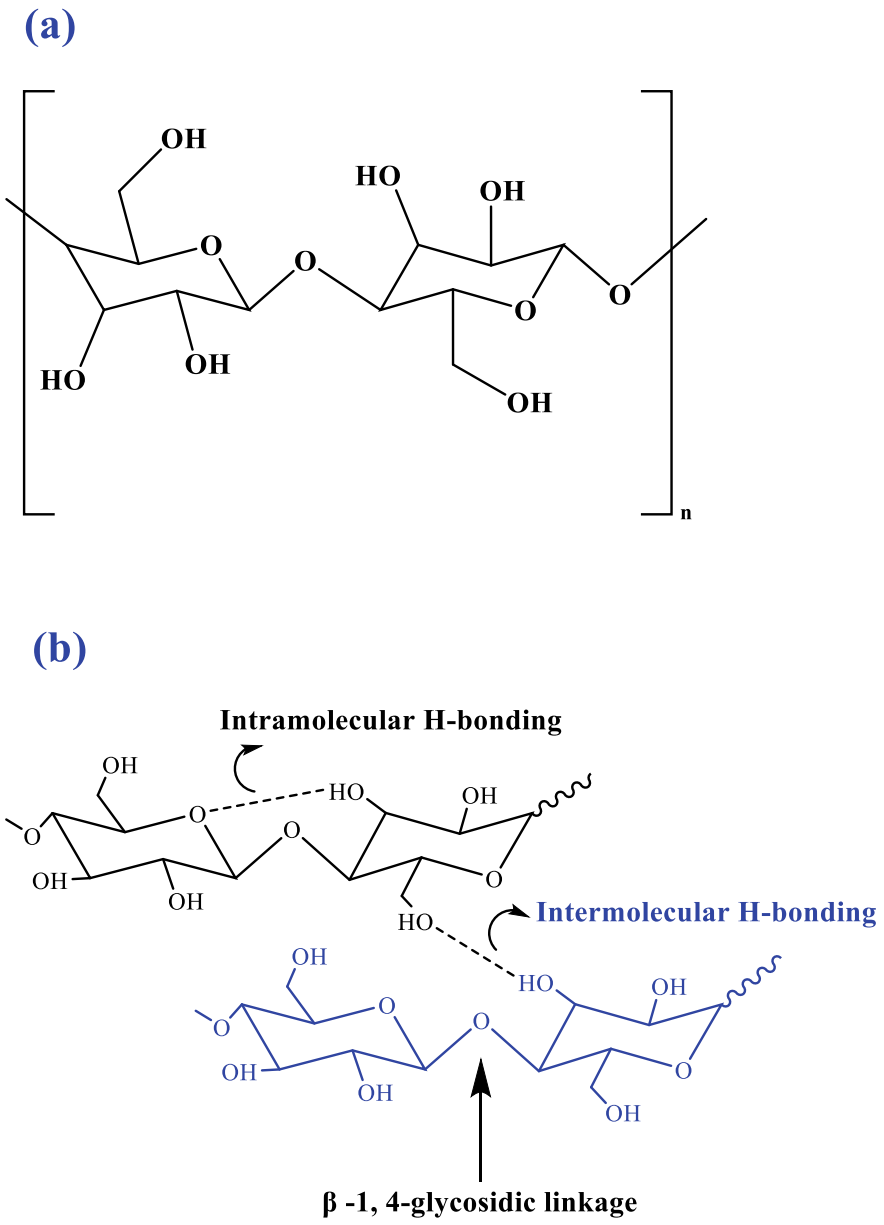

Fig. 1 **a** Molecular structure of cellulose (n = Degree of polymerization, DP), **b** intramolecular and intermolecular hydrogen bonding in cellulose molecules

solvents due to its dense intermolecular and intramolecular hydrogen bond networks (Fig. 1b), tightly packed chains with van der Waals interactions, and partially crystalline structure [13, 14]. The intramolecular hydrogen bonds provide chain stiffness, while intermolecular hydrogen bonds allow the linear polymer molecules to assemble in sheet-like structures [15]. The opening move to overcome these challenges was introducing the viscose process of cellulose dissolution. However, environmentally unfriendly processing and lower mechanical properties of the RC impeded their extended application for functional purposes. Numerous solvents and multiple technologies have been subsequently discovered for fabricating regenerated cellulose-based fibers, films, beads, hydrogels, aerogels, and composite materials, indicating their potential applications in packaging, textiles, water treatment, optical/electrical devices, biomedicine, etc. These regenerated cellulose-based materials exhibit good performances and excellent biodegradability, showing immense potential as environmentally friendly materials to substitute part of the nonbiodegradable materials. Therefore, the utmost goal of current research in this area is to develop regenerated cellulose-based materials with improved functionalities. This book chapter has been designed to summarize various shaping of regenerated cellulose-based materials and composites. Herein, we have provided an overview of recent progress in cellulose dissolution, synthesis process, properties, and potential applications of regenerated cellulose-based materials and composites. We have concluded this book chapter by addressing the challenges and future research opportunities in this domain.

2 Preparation of Cellulose

Before dissolving the cellulose, removing the impurities from the cellulose sources is obvious. For instance, cellulose extraction from lignocellulosic biomass needs extra chemical treatment to remove impurities (wax, lignin, and hemicellulose) and make cellulose suitable for dissolution since residual lignin and hemicelluloses result in higher roughness surface structure of RC-based products [15]. Wax components can be removed by refluxing biomass with toluene–ethanol mixture in a soxhlet apparatus. Steam explosion treatment (by saturated steam) at a temperature of 195 °C for 5 min in a stainless-steel reactor can also partially decrease lignin [16]. However, most lignin and hemicellulose components can be removed after treating lignocellulosic biomass with sodium chlorite and alkaline solutions to extract almost pure cellulose [17].

Interestingly, some strong oxidizers (nitric acid) can also oxidize lignin to form nitric lignin, which can be dissolved in the post-treated NaOH aqueous solution. Furthermore, hydrogen peroxide addition generates other active radicals, such as hydroxyl radicals (HO) and superoxide anion radicals (O_2), which participate in the delignifying and bleaching, and so it has been successfully used to isolate lignin and hemicellulose from agricultural residues [13, 18]. After removing a great part of the initial noncellulosic components, visually white-colored cellulose can be obtained [17]. Conversely, the preparation of RC from waste garments requires the removal

of the easy-care finish since their presence dramatically reduces the solubility of the waste garments in the solvent. It has been reported that treatment of garments in acid/alkaline conditions can strip off the easy-care finishes and escalate solubility [19–21].

3 Dissolution and Regeneration of Cellulose

Breaking hydrogen bonds is the key to dissolving cellulose [22]. Dissolution of cellulose is commercially conducted by the viscose process or lyocell, carbacell, MDCell, and ionic liquid process [2, 23, 24]. Therefore, these processes have their respective advantages and problems for which research and development for novel solvents are currently ongoing [23, 24]. Table 1 elucidates the advantages and disadvantages of different cellulose dissolution methods.

The most applied industrial process to dissolve cellulose is the viscose process developed in the late nineteenth century and where cellulose needs to be reacted with carbon disulfide (CS_2) and sodium hydroxide to form cellulose xanthate and then converted back to pure cellulose in acidic coagulation bath [25]. To date, several solvents have been investigated considering the green alternatives to the traditional cellulose solvents.

Among other techniques, the lyocell process is a promising environmentally friendly alternative to the conventional viscose process that emerged in the early 1990s. Nontoxic N-methylmorpholine-N-oxide (NMMO) is typically utilized as a solvent in the lyocell process for direct cellulose dissolution and can be recycled with a greater than 99% recovery proportion [26–29]. In this process, cellulose is dissolved at constant mixing with increasing temperature and reduced pressure to dehydrate the tertiary mixture of NMMO, water, and cellulose into cellulose-NMMO solution [30–32]. However, the dissolution process requires special precautions to protect the solvent from oxidation, or antioxidants can be added during the dissolution process [33, 34].

Another technology that has raised attention in recent years is the Carbacell process which has been utilized as an environmentally friendly alternative for cellulose dissolution. This process relies on forming cellulose carbamate (CC), which is easily obtained by reacting cellulose with urea. As a regeneration bath, diluted acid or a sodium carbonate solution is used [35–37]. In this system, alkali hydrates and urea complexes (NaOH/urea and LiOH/urea) play critical roles in dissolving cellulose. Alkali hydrates attach to the hydroxyl groups of the cellulose to build new hydrogen bonding networks at low temperatures (Fig. 2b). At the same time, the urea hydrates may self-assemble at the surface of the NaOH hydrogen-bonded cellulose to form an inclusion complex (IC), resulting in excellent dissolution (Fig. 2a). Furthermore, a worm-like cellulose IC enclosed by urea hydrates exists in the cellulose solution. Nonetheless, the cellulose solution is volatile and can be very sensitive to temperature, polymer content, and the storage period, resulting in aggregations [38–41].

Table 1 Advantages and disadvantages of different cellulose dissolution methods

Process	Solvent	Advantages	Limitations	Refs.
Viscose	NaOH, CS_2	Major commercial process Widely used Results in high-performance fibers	Harmful to the environment, complex processing, need to use CS_2, hazardous byproducts (H_2S, COS), challenging to recycle, high water consumption, and cannot dissolve high DP cellulose	[28, 36]
Lyocell	NMMO	Environment conscious process Nontoxic solvent Recyclable with almost >99% recovery proportion Little effluent generation	Uses thermally volatile solvent, requires activation before dissolution, high water, and power consumption for solvent and water recovery, demands harsh conditions, expensive process, requires safety technology, unable to dissolve high DP cellulose, the need for stabilizers to control oxidation	[26–29, 183]
Carbacell	NaOH/Urea	Nontoxic solvent Ecofriendly process Low cost and simple process	Inferior material properties Difficult solvent recovery	[35, 48, 74]
Ionic liquid	IL (e.g., [bmim]OAc [DBNH]OAc BMIMCl EmimAc AMIMCI, etc.	Ecofriendly process, effective for organic/inorganic polymers, tunable physical and chemical properties of the solvent, such as-wide melting point range (−40 to 400 °C), lower vapor pressure, melting point, and flammability, thermal stability (up to 400 °C), nonvolatility, nonexplosiveness, similar technologies as NMMO process, potential industrial applications, improved mechanical properties results in high-performance materials and can dissolve high DP cellulose, easy recycling	High overall costs Solvent recovery requires extra energy	[25–27, 183, 184]

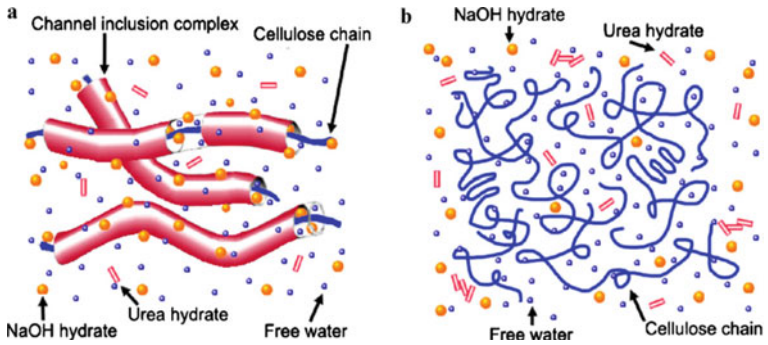

Fig. 2 Schematic diagram of the regeneration mechanism in Carbacell process. **a** Formation of IC channel, cellulose inclusion complex hosted by urea exists in NaOH/urea aqueous solution to form homogeneous cellulose solution, **b** aggregation and regeneration of cellulose gel sheet. Republished with permission from [40]

As a new nonderivatizing and green solvent class, ionic liquids (ILs) consisting entirely of anions and cations have recently received much attention for cellulose dissolution due to their unique properties. First, ionic liquid enters the space between the cellulose chains. Then, during dissolution, the cellulose's inter- and intramolecular hydroxyl groups are replaced by hydrogen bonds or coordination bonds formed between IL and the cellulose's hydroxyl groups [42]. However, the dissolution of cellulose depends on the nature of IL. For example, the solubility of cellulose and dissolution rate in EmimAc is slightly higher than in AmimCl due to its low viscosity, which facilitates good dispersion of cellulose [13]. In addition, several factors influence the cellulose dissolution and regeneration while using IL, such as reaction time, temperature, drying procedure, antisolvent, sample degree of polymerization and purity, and solvent structure [17, 43].

Another promising solvent for cellulose dissolution is the deep eutectic solvents (DESs), a novel class of solvents, catalysts, and reagents. These are related to more well-known ionic liquids and share high solvent capacity and low-vapor pressure characteristics. Compared to ionic liquids, DESs are easily obtained from cheap and widely available chemicals by simply mixing at elevated temperatures. Furthermore, numerous DES ingredients can also be found in nature, and DESs are known to have low toxicity and are many times more biodegradable than ionic liquids. Recently, guanidine hydrochloride and anhydrous phosphoric acid (molar ratio of 1: 2) have been used as DES at room temperature to dissolve wood cellulose fibers and microcrystalline cellulose. The decrease in DP of cellulose due to the highly acidic medium is the driving force for this dissolution [44].

The MDCell process, named after both inventors, is a novel cellulose dissolving process that deals with the preparation of RC by direct dissolution of cellulose in aqueous tetrabutylphosphonium hydroxide (TBPH) (Fig. 3). High-purity RC powders and films can be fabricated using this method. In the coagulation step, organic carbonates such as propylene carbonate [3] are employed as promotors. This

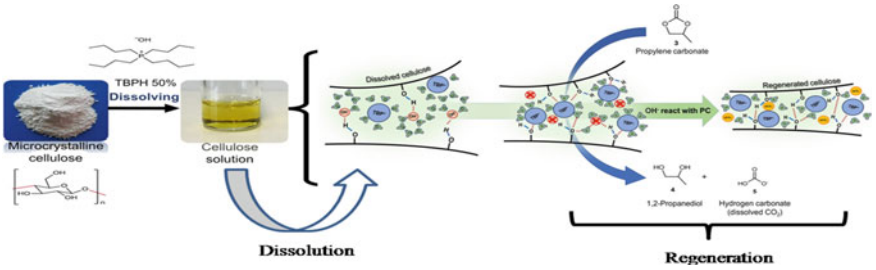

Fig. 3 Mechanism of cellulose dissolution, $[OH]^-$ of TBPH breaks the strong hydrogen bonds between the cellulose chains leading to cellulose dissolution. However, a nucleophilic attack of the ions occurs in the presence of propylene carbonate and generates 1; 2-propanediol [4] and hydrogen carbonate [5]. Thus, no $[OH]^-$ are available to stabilize the dissolved cellulose, and the H-bonds are rearranged between the cellulose chains. Republished with permission from [2]

approach is simple, rapid, does not require the use of inert gas, can be performed at room temperature, and is environmentally benign. All the compounds used are harmless and may be derived from CO_2 fixation (organic carbonate) or are recyclable ($[TBP]^+$). In addition, water is acceptable at every stage [2].

Apart from this, a novel cellulose dissolution system has been reported recently named the green viscose system. It is based on using a CO_2 switchable solvent consisting of a superbase [1,8-diazabicyclo [5.4.0] undec-7-ene (DBU)] and polar and aprotic cosolvents [dimethyl sulfoxide (DMSO)]. This method can dissolve cellulose using either a nonderivative or a derivative strategy (with or without alcohol). Interestingly, this derivative approach is similar to the viscose process [45]. Figure 4 illustrates the general features and advantages of the green viscose process.

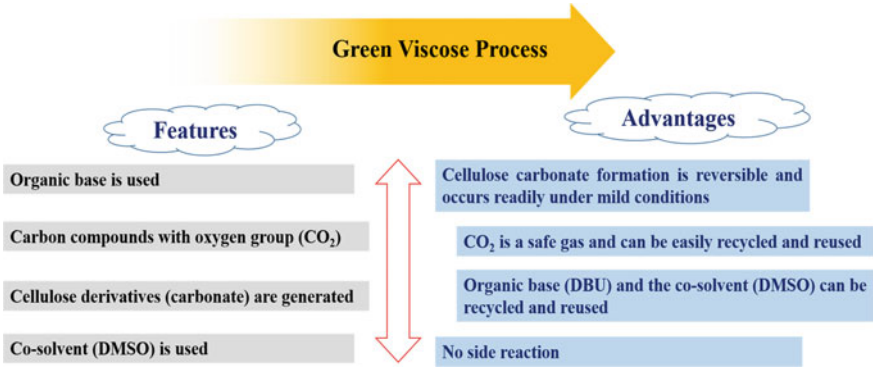

Fig. 4 General features and advantages of the green viscose process, Idea was taken from [45–47]

3.1 Properties of RC

The regeneration process converts cellulose-I to cellulose-II, and the breakage of the β-1, 4-glycosidic bonds of the cellulose chains causes the degradation of cellulose. Thus, the decrease in DP and cellulose crystallinity occurs after the regeneration process. However, with the increase in the temperature, the DP value is significantly decreased [13, 17]. It has been reported that DP of cellulose (cotton pulp) remarkably reduced from 510 to 180 within seven hours when dissolved in ([bmim]Cl) [48]. The decrease of DP and the presence of microvoids in the cellulose structure are responsible for the lower mechanical strength of RC [49]. Small-angle X-ray scattering (SAXS) technique has been widely used to investigate the structure of microvoids till now [50–58]. Additionally, it can measure the cord length, the radius of gyration, mean cross section, and microvoid volume fraction [56, 59]. Nevertheless, SAXS measurements alone are insufficient to correctly characterize microvoid dimensions and their volume fraction. Hence, combining medium-resolution small-angle neutron scattering (MSANS) with SAXS experiments allows microvoids to be modeled as elongated cylinders, and the void volume fractions can be estimated frequently [60].

Another critical aspect of determining the function ability of RC is its molecular orientation. A plethora of reliable quantitative methods for the characterization of molecular orientation in cellulosic and other polymeric fibers exist to investigate molecular directions, such as rotor synchronized magic angle spinning (ROSMAS) or DECODER NMR spectroscopy, wide angle X-ray scattering (WAXS), infrared (IR) dichroism, birefringence, and polarized Raman spectroscopy, each method having advantages and limitations [61–67]. Recently, a unique way of evaluating polarized Raman studies to identify the molecular orientation of RC fibers has been developed, based on replacing the Legendre polynomial approach with a wrapped Lorentzian function calculated from X-ray scattering patterns. This approach eliminates the necessity for right-angle scattering studies [68].

4 RC-Based Materials

4.1 RC Fiber

Fiber is the material of most significant industrial importance among regenerated cellulose-based materials. RC fibers are generally spun through wet spinning and dry-jet wet spinning processes [23, 24]. During the wet spinning process, the polymer solution is extruded directly into a coagulation bath via the spinneret (Fig. 5a). However, after coagulation, molecular alignment and orientation can be optimized by employing numerous drawings or baths after coagulation. Contrarily, dry-jet wet spinning, a modified version of wet spinning, deals with the extrusion of polymer solution through an air gap before the coagulation process rather than directly into

the bath and can result in greater molecular alignment compared to conventional wet spinning (Fig. 5b) [69].

Viscose fiber spun through the wet spinning route has outperformed others due to its unique fiber quality and wide range of fiber types ranging from standard fibers to cotton-like modal and polynosic fibers, as well as firm technical performance as tire cord [60]. However, unfavorable processing conditions led the researchers to consider alternatives. As an efficient option, wet spun or dry–wet spun lyocell fiber embodies high elasticity and regain, providing shape ability and comfort to the garments [70]. However, the structure and formation of the spun fibers are affected by the dissolution, spinning, and regeneration conditions (hydration number of solvent, rheological parameters such as DP, viscosity, and cellulose concentration) [30, 71, 72]. Even though the fibers have a compact structure, a few microvoids in the cross sections impair the mechanical properties [73]. Furthermore, the fibers are prone to fibrillation under mechanical and moist circumstances because of the fibrils' high degree of orientation and weak intrafibrillar hydrogen bonding [33, 34].

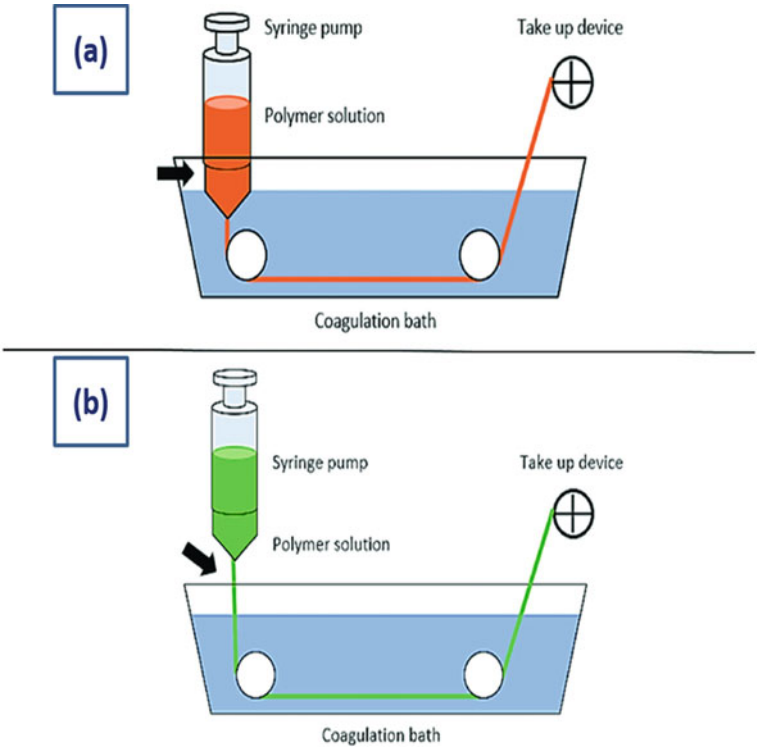

Fig. 5 Schematic diagrams of **a** wet spinning and **b** dry-jet wet spinning. Republished with permission from [69]

On the other hand, fiber synthesis by carbacell process can be done through the wet spinning process, similar to those in viscose plants which deal with spinning solutions containing cellulose carbamate to reduce the usage of CS_2 [35–37]. However, the resulting fiber qualities were not comparable to those of standard viscose and did not initially achieve the tenacity of modal or other modified viscose fibers. Due to this, despite multiple advances, the cellulose carbamate process failed to be commercialized [74]. Research is being conducted to develop fiber with improved spinnability, primarily dependent on the frequent solubility of CC and the elimination of microvoids [75]. In a recent study, nitrogen- and sulfur-free RC filaments were spun on a pilot scale from cellulose carbamate in a NaOH/ZnO aqueous solution utilizing a one-step acid coagulation procedure. The presence of ZnO enhanced the solubility of CC considerably. Furthermore, microvoids in the fiber structure rapidly disappeared after multidrawing and drying procedures, resulting in a denser cellulose II crystal structure [76].

Ioncell fiber is spun the same way as lyocell fiber, but the NMMO is substituted with ionic liquid. The ability to attain greater draw ratios when spinning from the IL can improve the mechanical properties of ioncell fiber [77]. In this process, dissolved cellulose (without any derivatization) is regenerated as continuous filament by the wet spinning or dry-jet wet spinning process. Moreover, physicochemical changes of biomass resulting from the action of different pretreatments (alkaline, hydrothermal, and acidic pretreatments) can be advocated to improve the dissolution of cellulose in ILs, such as surface area, hemicelluloses removal, crystallinity, and reduced DP for cellulose [25, 78]. The mechanical properties of the ioncell fiber are strongly influenced by the chosen spinning parameters (extrusion velocity, draw ratio, air gap, spinneret geometry, after treatment) as well as the properties of the raw material (cellulose and hemicellulose contents, intrinsic viscosity, polydispersity index, molar mass distribution [27, 79, 80]. Table 2 delineates the distinct factors essential for the spinnability of IL-based RC fibers. Therefore, the improved and customizable mechanical qualities have made it appropriate as a reinforcing material in composite structures and other technological applications as a high-performance and functional fiber [5, 22, 74, 81, 82]. Table 3 summarizes the mechanical properties of some recently synthesized RC fibers.

4.1.1 RC Fiber by Closed Loop Recycling

Addressing the scarcity of raw materials for fiber production, researchers have proposed closed loop recycling as an alternative to mechanical recycling, in which polymers are depolymerized into monomers and commercially repolymerized into new filaments for textile applications. It involves transforming cotton-based waste garments into second-lifetime cellulosic fiber [83]. A recent study on closed loop recycling of cellulosic waste garments has explored using the garments as feedstock for fiber regeneration via the lyocell process [19, 20]. The fibers have higher physical, mechanical, and molecular qualities than ordinary fibers regenerated from wood pulp. Additionally, a suitable blend of wood pulp and pulp salvaged from

Table 2 Factors important for spinnability and physical/mechanical properties of IL-based RC fibers

Factors		Consequences	Refs.
Raw material properties	Polydispersity index (PDI)	Influences the rheological behavior of spinning solutions Minimum PDI shows enhanced spinnability	[27]
	Molecular weight & DP	Tensile strength shows a linear relation with DP within a certain limit An increase in molecular weight improves tensile strength through increasing chain entanglements	[5, 26]
	Diffusion coefficients of solvent	Crystallinity, strength, and elongation-at break decrease with the increase in the diffusion coefficient of solvent	[81]
	Viscosity of spinning dope	Increased viscosity within a certain limit significantly improves the spinnability and thus the final mechanical properties of the spun fibers	[5]
Spinning parameters	Draw ratio	Higher draw ratios result in improved cellulose chain orientation and mechanical properties (higher crystallinity, decomposition temperatures, and stability)	[22, 26]
	Environment of the air gap	Low temperature and low relative humidity in the air gap result in fibers with a high tensile strength at a high draw ratio	[22]
	Choice of nonsolvent in the coagulation bath	Nonpolar nonsolvents reduce crystalline cellulose by preventing molecular stacking through hydrophobic interactions Inversely, polar nonsolvent (water) results in regeneration by coagulation to semicrystalline cellulose II in the dry state	[184]

Table 3 Mechanical properties of the recently synthesized RC fibers

RC fiber	Solvent used	Tenacity	Elongation (%)	Modulus	Refs.
Lyocell	NMMO	D-34.7; W-28.8 (cN/tex)	D-11.2; W-13.2	D-205; W-112 (cN/tex)	[70]
RC-1 from plain woven cotton	NMMO	D-48.7; W-42.4 (cN/tex)	D-9.2; W-11.0	D-303; W-152 (cN/tex)	[70]
RC fiber from waste denim	NMMO	D-42.5; W-35.2 (cN/tex)	D-9.7; W-14.2	D-298; W-162 (cN/tex)	[70]
Lyocell from cellulose pulp	NMMO	D-4.29, W-2.75 (cN/dtex)	13.1	88.3 (cN/dtex)	[185]
Cotton lint (DP-2680 ± 26)	NMMO	186.5 MPa	21.4	8.63 GPa	[26]
Cotton lint (DP-2124 ± 20)	NMMO	184.3 MPa	21.6	8.11 GPa	[26]
Cotton lint (DP-646 ± 12)	AMIMCl	70.6 MPa	12.2	6.14 GPa	[26]
Cotton lint (DP-495 ± 14)	AMIMCl	57.5 MPa	10.4	5.90 GPa	[26]
Wood pulp (DP-851 ± 14)	AMIMCl	98.6 MPa	12.8	5.85 GPa	[26]
RC fiber from Lignocellulosic biomass, eucalyptus (*E. urophylla*)	[bmim]OAc	2.01 cN/dtex	5.26	–	[25]
Ioncell-F fibers	[DBNH]OAc	D-58; W-57 (cN/tex)	–	34 GPa	[74]
High performance RC fiber	BMIMCl	1.15–0.08 GPa	5.5	42.9–2.8 GPa	[5]
IL-cell from cellulose pulp	BMIMCl	D-3.54, W-2.59 (cN/dtex)	7.24	75.1 cN/dtex	[185]
RC filaments	NaOH/urea/ZnO	2.36 cN/dtex	–	–	[76]
Fibers regenerated from blue cotton t-shirt	LiOH-urea	1.23 cN/dtex	15.78	149 MPa	[41]
Viscose from cellulose pulp	LiOH-urea	D-2.15; W-1.41 (cN/dtex)	22.6	35.7 cN/dtex	[185]

(continued)

Table 3 (continued)

RC fiber	Solvent used	Tenacity	Elongation (%)	Modulus	Refs.
Newdal from cellulose pulp	LiOH-urea	D-2.84, W-1.70 (cN/dtex)	22.6	46.9 cN/dtex	[185]

D-Dry; W-Wet

cotton-based waste clothing can yield fibers with qualities intermediate to cotton and lyocell. The higher storage modulus, total crystallinity index, and lower order index of fibers regenerated from waste cotton garments are associated with a higher degree of polymerization. However, higher degradation of the waste garments during their wash/wear lifetime may lower the molecular mass [21, 70]. Surprisingly, fibers regenerated from cotton waste exhibit supramolecular properties similar to traditional lyocell fibers, which investigate the interactions of the cellulose polymer molecules within the polymer chains and with neighboring chains, the degree of order of the chains, and the crystalline proportion in the fibers [21] (Table 4).

Table 4 Mechanical properties and dissolving conditions of the recently synthesized RC films

Source of cellulose	Solvent used	Dissolving condition	Mechanical properties			Refs.
			Tensile strength (MPa)	Elongation at break (%)	Modulus (MPa)	
Oil palm empty fruit bunch	BMIMCl	90 ± 2 °C for 24 h	71.5 ± 4.4	6.6 ± 0.5	–	[1]
Pine, cotton, bamboo cellulose, and microcrystalline cellulose (MCC)	EmimAc	80 °C for 0.5 h	Cotton-120 MCC-69	–	–	[15]
Borassus fruit fibers	AmimCl	80 °C for 2 h	111 ± 19	3.1 ± 0.8	6149 ± 603	[17]
Cotton pulp	[bmim]Cl	90 °C for 7 h	–	–	–	[48]
Cotton linter	EmimCl	80 °C–120 °C	119	8.8	–	[84]
Corn husk	AmimCl EmimAc	80 °C for 2 h 120 °C for 12 h	120 47	4.1 1.4	6000 4100	[13]
Cotton linter pulp	NaOH/urea	Ambient temperature for 5 min	139	4.44	–	[40]
Cellulose pulp	NaOH, CS_2	30–35 °C for 4 h	44.97	–	1955.10	[16]

4.2 RC Film

With the substantial "white pollution" caused by nonbiodegradable plastic films, considerable emphasis has been directed toward developing renewable and biodegradable RC-based film materials as alternatives to petroleum-derived materials [15]. Due to their excellent properties, biodegradable nature, and overall good film forming ability, RC Film may offer potential applications in various industries, including transparent, biodegradable food packaging, agricultural, wrapping purposes, functional materials, medical goods, flexible electronic devices, and optoelectronic applications. In general, RC film is developed by solvent casting and finally coagulating the degassed cellulose solvent mixture in nonsolvent [1, 11, 14, 15, 17, 84, 85]. RC films display a homogeneous and smooth surface which indicates a higher molecular orientation degree of the cotton film obtained by the regenerated process. Some small nodules and contours in the cellulose film may result from strong hydrogen bonds of cellulose [13, 15, 84, 86, 87]. Furthermore, the RC film contains an amorphous structure, which promotes water absorption and biodegradability but decreases mechanical behavior [17]. The solvent used for cellulose breakdown significantly impacts the mechanical properties of RC film. Ionic solvent-based RC films exhibit higher tensile strength and modulus than other RC films. Sometimes it is higher than the commonly used commercial polyolefin films, such as polyethylene and polypropylene, which have a range of 20–40 MPa [13, 17].

4.2.1 Functional RC Film

Although research has been conducted to make RC-based biodegradable films, the brittle characteristic, poor processability, poor mechanical behavior, and water sensitivity remain significant issues that limit their usage in various functional applications [11, 14, 48, 84]. Increasing the DP values improves thermal stability and tensile properties of RC films. More robust and flexible films can be produced with increased cellulose crystallinity having denser and more uniform cross sections [15, 84, 88, 89]. Furthermore, adding aromatic heterocyclic organic compounds can also minimize DP loss of RC and improve mechanical properties of films. Recently, N-methylimidazole (NMI) has been added into [bmim]Cl as an additive. Because of the steric hindrance, NMI enters the gap between cellulose chains more frequently than [bmim] Cl. In addition, it is difficult for $[bmim]^+$ cations to attack the oxygen atom of the β-1, 4-glycosidic bonds of the cellulose chains due to the lower concentration. So, the β-1, 4-glycosidic bonds remain harder to break. Therefore, RC developed from the mixture of [bmim]Cl and NMI shows much higher DP than conventionally produced RC from pure [bmim]Cl [48].

Plasticization is another simple and effective way to improve the chemical or physical properties of RC film. Incorporating different plasticizers (sorbitol, glycerol, and carboxymethyl cellulose) with an ionic liquid solvent can improve the

hydrophobicity, mechanical, and thermal properties of RC films. However, the roughness of the plasticized cellulose films increases in the presence of plasticizers. The increased hydrophobicity (reduction of surface energy) of RC films is related to their morphology and the inter- and intramolecular hydrogen bonding within the cellulose hydroxyl groups and plasticizers; this increases the contact angle value of the blends and makes plasticized cellulose films useful for packaging. Additionally, the tensile stress of the plasticized cellulose films increases due to the formation of new hydrogen bond networks and stacking interactions between cellulose and the different plasticizers [11, 86, 90, 91].

Adding a crosslinker with solvent is another approach to forming RC films with improved physical, mechanical, and thermal properties. Crosslinked RC film shows a more compact structure due to complex networks and the reduction of molecular movements. For example, citric acid (CA), when added at a plateau level (10 wt%) as a crosslinker with EMIMCl, improves the thermal stability of RC films. Because of its high compatibility, CA can pass between the RC chains and disrupt the intermolecular connections, forming bonds with the polymer chains to produce a compact structure. However, a more open H-bonding network is formed at higher CA concentrations (more than 10 wt%), resulting in lower film stability due to increased free volume and decreased chain entanglement. In addition, crosslinked films exhibit increased hydrophilicity because of the abundance of highly polar groups under this state [14, 92–94].

4.3 RC Gel

Upon being soluble, cellulose can be regenerated into gel (hydrogel, aerogel, cryogel) form [95]. For example, by simply disrupting the hydrogen-bond network using phosphoric acid, the RC can be molded into gelling material and emulsion stabilizer [96].

4.3.1 RC Hydrogel

Hydrogels are polymeric materials that swell with water and have a distinct three-dimensional network and different physical properties such as tissue-like elasticity and mechanical strength [97]. The freeze–thaw, sol–gel, or chemical crosslinking methods are often used to synthesize RC hydrogel. In the crosslinked RC hydrogel, polymers are chemically crosslinked via intermolecular and intramolecular covalent bonding. The presence of a crosslinker not only eases the formation of hydrogel but also makes the structure more rigid. Therefore, the improved mechanical stability of hydrogel can be attributed to the crosslinked networks and the water content of cellulose. The addition of cellulose derivatives (Na-carboxymethylcellulose) enhances the function of covalent bonding and imparts a denser crosslinked network with less water content in the hydrogel structure. Additionally, it affects the viscosity of the solution

and thus effectively improves the mechanical stability of the hydrogel. Furthermore, the volume of the hydrogel increases with soaking time due to continual internal stress, resulting in thinning of the crosslinked network wall. However, a more significant concentration of cellulose derivatives disrupts the homogeneity of the cellulose solution due to partial dissolution and reduces hydrogel transparency [95, 98–100].

4.3.2 RC Aerogel

RC aerogel (RCA) is synthesized by a lyophilizing or freeze-drying process. In this process, water is removed from the cellulose hydrogel, frozen, and placed under a vacuum, allowing the ice to transform directly from solid to vapor without passing through a liquid phase. The process consists of three distinct yet interrelated steps: freezing, primary drying (sublimation), and secondary drying (desorption) [101]. The morphology of synthesized RCA changes with the gelation duration and temperature, and it can be functionalized by including a functional side group into the RCA chain. The beauty of the 3D network skeleton inside the RCA is its use as a template for preparing carbon aerogel [102]. Although the resorcinol–formaldehyde system is the most utilized raw material for constructing carbon aerogels, its high density (100–800 mg cm^{-1}), fragility, toxicity, and environmental contamination severely limit the development and industrial application of this class of carbon aerogels [103, 104].

An alternative green route of synthesizing black carbon aerogel is the pyrolysis of freeze-dried RCA at elevated temperatures under the argon atmosphere. Although the pyrolysis process decomposes oxygen-containing functional groups and destroys the crystalline structure of cellulose to generate highly disordered amorphous graphite, the nanoporous carbon aerogels retain their crosslinked 3D network after pyrolysis [105]. Meanwhile, synthesized carbon aerogels exhibit high hydrophobicity, electrical conductivity, and flame retardancy, making them potentially valuable for waterproof materials, electronic devices, and flame retardants. Figure 6a shows that carbon aerogel with a WCA of 139° can stably hold numerous water drops on the surface, suggesting the formation of superhydrophobicity. It may be employed as high-performance separating or adsorbing materials for oil spill and chemical leak cleaning. Moreover, cellulose aerogels have low conductivity when connected to a closed-circuit system and cannot support current flow leading to no luminescence of the bulb (Fig. 6b). On the other hand, carbon aerogels are good electrical conductors, allowing current to flow through and light the bulb. The bulb's brightness is comparable to that of the bulb in the circuit with aluminum mesh, which may find applications in electronic equipment. Carbon aerogels are also superior fire retardants, which do not support burning and release noticeable smoke all the time when exposed to a flame of an alcohol burner (Fig. 6c) [106].

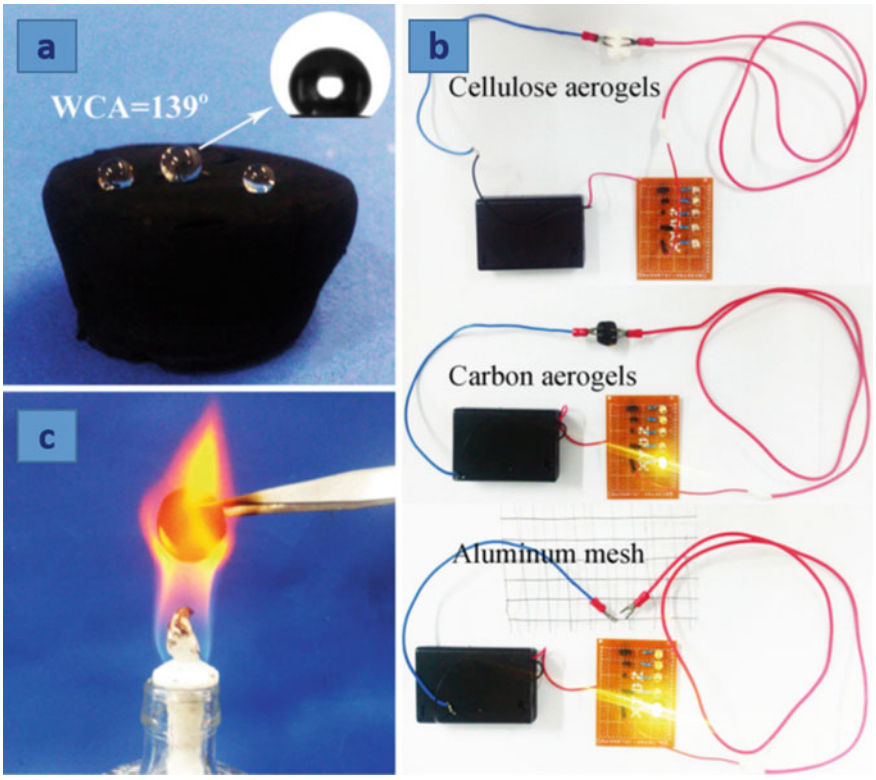

Fig. 6 **a** Hydrophobic carbon aerogels, **b** determination of electrical conductivity of cellulose aerogels, carbon aerogels, and aluminum mesh. **c** Digital photograph of the carbon aerogel in a hot flame of an alcohol burner. Republished with permission from [106]

4.3.3 RC Cryogel

RC cryogel is an aerogel-like material that can be synthesized by freeze-dried method of the swollen hydrogel. The swelled hydrogel is frozen and freeze-dried to conserve the endoskeleton microstructure of a hydrogel after swelling and produces a skeletal structure known as cryogel. Cryogel, originating from cellulose-based materials, is biodegradable. Furthermore, high water content absorbed by hydrogel generates cryogel with increased pore size, which substantially affects the thinning of crosslinked network wall, volume, and stability of cryogel structure. In a recent study, macroporous cryogel was prepared using freeze-dried methods from the swollen hydrogel. When the swollen hydrogels are frozen, the frozen and thinner crosslinked network wall is disrupted by the crystallization of water in the hydrogel during the freezing process. Larger ice crystallites formed when the hydrogel steadily froze in the freezer, destroying the cryogel crosslinked network wall. The devastation occurs because the frozen water's volume expands toward the frozen crosslinked network

wall. Furthermore, small holes are formed on the wall of the crosslinked network to interconnect with the macropores on cryogel. This super lightweight and adsorptive cryogel is suited for use in agricultural sectors as an alternate medium for fertilizer transfer and improves soil water retention [95, 107–109].

4.4 RC Membrane

Membrane plays a significant role in industrial applications, such as separation (dialysis, ultrafiltration, fractionation) and purification technology for gas separation and sewage treatment, packaging technology for food and others, and biomedical technology for wound healing and tissue engineering [110]. The RC membrane is a versatile platform for surface modification due to the presence of hydroxyl groups and can be used for recovering hemicellulose (galactoglucomannan) and plant sterol (phytosterols) from plant materials [111, 112].

4.4.1 Adsorptive Membrane

Although the adsorptive membrane has the dual function of adsorption and filtration, it depends on the adsorption process in which the substances are bounded by chemical and physical interactions with solid surfaces [113]. Surface modification of cellulose through grafting polymerization is a practical approach to producing the adsorptive RC membrane. Adsorptive RC membrane has wide applications in separation technology, protein purification, and other biotechnological fields [114, 115]. It has also been thrivingly used as a precursor in producing carbon hollow fiber membranes through the carbonization process for their advanced application in gas permeation [116]. Recently, an adsorptive membrane has been synthesized by grafting poly (glycidyl methacrylate) on the RC membrane via the surface-initiated atom transfer radical polymerization process. N-methylglucamine was combined with epoxide rings to form poly hydroxyl functional groups, which functioned as the main boron binding sites and increased boron binding capabilities. Under neutral pH conditions, the modified membrane's maximum adsorption capacity was determined to be 0.75 mmol/g, comparable to commercial resins [114]. However, as the cellulose content rises, the pore size of the RC membrane decreases, lowering the membrane's permeability [117].

4.4.2 Antimicrobial Membrane

Because of their polysaccharide nature and lack of biocidal groups, RC membranes are rapidly contaminated by bacteria, limiting their long-term use. Consequently, developing RC membranes with antimicrobial surfaces and high mechanical strength has gained tremendous interest from researchers and industrialists worldwide.

Many antibacterial compounds such as silver and silver chloride nanoparticles, chitosan, quaternary ammonium, benzalkonium chloride, zinc oxide nanoparticles, and triclosan have been mixed to boost the antibacterial capabilities of cellulose membranes. Chemical grafting is the most successful mixing method that prevents the possible release of residual toxicity and minimizes additional environmental impact [118]. In a recent study, aminosilanes with different concentrations have been grafted with RC membranes. The grafted RC membranes had high mechanical strength of 65.2–93.5 Mpa, high hydrophobicity, and thermal stability. Additionally, grafted RC membranes with the most amino groups and the longest aminoalkyl chain are more efficient against Gram-positive bacteria. However, the bacteria-killing ratio increased with improving amino content and reached almost 100%. The translucent RC membranes developed with excellent tensile strength, thermal stability, and enhanced antibacterial capabilities may open new possibilities for innovation and applications in packaging [110].

4.5 RC Microspheres/Beads

RC microspheres have attracted enormous research attention because of their widespread applications in biomedical or environmental remediation (water and protein purifications as biosorbent, fractionation of polymers as chromatography packing, biocatalyst, drug delivery, and electrode materials) both at laboratory and industrial scale due to their tunable properties, large surface area, porosity, and abundant hydroxyl groups [119–121]. Cellulose microspheres can be synthesized in three steps: dissolution, shaping, and solidification [122, 123]. In recent studies, mainstream shaping techniques, including dropping and emulsion (Fig. 7) coupled with certain solidification (coagulation) techniques, were employed to prepare microspheres [124–128].

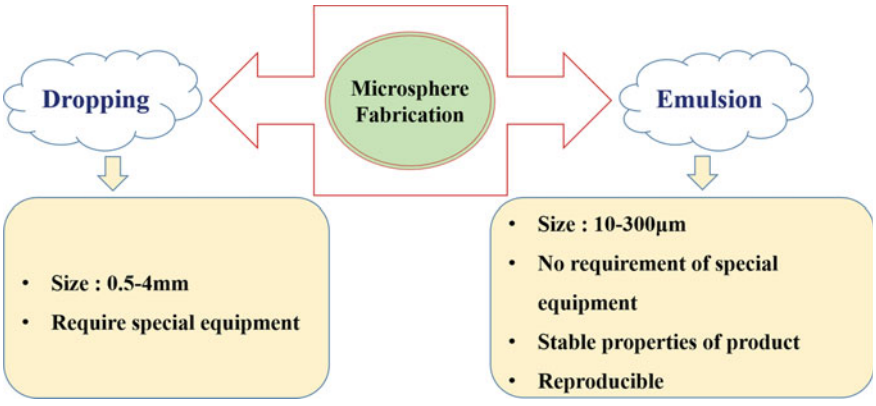

Fig. 7 Fabrication process of RC-based microsphere, Idea was taken from [119, 128]

In the emulsion process, cellulose solution is combined with an immiscible organic solvent in surfactants (e.g., Span 80), forming a stable cellulose emulsion comprising droplets of the dissolved cellulose. Numerous factors, including the surfactant dosage, oil-to-water ratio, and coagulation conditions, affect the mean sizes, morphologies, and three-dimensional (3D) porous structures of cellulose microspheres. With a decrease in the dispersant dosage, oil–water ratio, and stirring speed, the size of the microspheres increased rapidly [120, 128]. In recent work, homogeneous and spherical porous RC microstructures (RCMSs) were synthesized by agglomerating micro/nanospheres in a pulp cellulose–tetraethylammonium hydroxide (TEAOH)/urea/H_2O solution using a simple emulsion–coagulation–oven drying procedure. Firstly, uniform micro/nanospheres were synthesized with a narrow size distribution of 600 nm–6 μm. Then the RCMSs were formed via the continuous agglomeration of the micro/nanospheres with increasing synthesis time. Synthesized RCMSs with cellulose II structure exhibited good physical properties, including high porosity (90–93%), pore volume (7.0–10.32 cm^3/g), and specific surface area (40–70 m^2/g) with chemical/thermal stabilities [119].

4.6 RC Nanomaterials

Nanomaterial is a novel class of materials commonly characterized as a solid structure with at least one nanometric dimension (less than 1000 nm). They have distinct properties than bulk particles due to their nanometric size [129]. The wide variety of properties is related to the high surface area, reactivity, and increased strength and are studied as drug carriers, antimicrobial materials, reinforcement agents, and optical materials, among other applications [130–133]. RC is one of the most important sources of natural polymeric nanomaterials and is widely used in composite materials as fillers because of their biodegradability, biocompatibility, renewability, lightweight, high aspect ratio, and most importantly, abundance. The RCNP can be synthesized by chemical, mechanical homogenization, enzymatic, and ultrasonication methods [134].

However, nanoparticle formation depends on the excellent dispersion of nanoparticles in aqueous suspension since cellulose tends to be aggregated after dissolution and regeneration. Therefore, many researchers have worked hard to focus on tackling the most challenging problems associated with dispersing cellulose in aqueous solutions without surfactants and modification. Among other cellulose dissolving solvents, NaOH-based solutions and urea are successfully introduced to improve both their solubility and the stability of the solution. This mechanism can be explained by the strong interaction with NaOH, which reduces cellulose molecule aggregation by forming new hydrogen bonds between cellulose and NaOH [135–137].

Another approach to producing RC nanoparticles is the dispersion of functionalized RCA in organic solvent (DMSO). The process is known as "self-assembly," where RCA acts as a template for RCNP formation and effectively avoids the solvent replacement process in traditional methods and simplifies the preparation process.

Tang Y and his research groups introduced polylactic acid side chains onto the cellulose chains to produce functionalized RCA. The van der Waals force among the cellulose molecular chains (especially the amorphous region) was weakened, which led to the swelling and dissolution of the connected zone by activating the organic solvent. Consequently, the FCNPs were disintegrated from FRCA and dispersed in DMSO. Eventually, FCNPs with good dispersibility and regular shape were prepared, which have uniform distribution (the average particle size is 37.2 nm), good thermal stability, and increasing hydrophobicity (water contact angle, WCA = 61.6°) and is an ideal candidate for polymer composite in terms of fillers [138].

5 RC-Based Composite

Incorporating functional nanofillers into the polymer matrix is a powerful tool to increase the polymer properties for an extensive range of applications, such as antistatic packages, shielding materials, electrodes, sensors, electric smart brands, and electromagnetic interference (EMI). Consequently, different nanofillers such as carbon nanotube (CNT), nanocarbon black, polypyrrole (PPy), boron nitride, graphene oxide (GO), nanohydroxyapatite, oxide, and nanoclay have been used to enhance the thermal and physical properties of RC [139, 140].

5.1 RC Composite Fiber/Filament

The tenacity of RC fiber is lower than cotton and some other synthetic fibers, which has induced the researchers to think about composite fiber. RC Composite fibers are composed of two or more inorganic and organic components involving organic cellulose as the fiber's backbone, while the inorganic component is responsible for the fiber's functionalization [141]. The fiber is spun by dry jet wet spinning, wet spinning, or electrospinning processes [142–144]. Incorporating GO/Reduced GO in RC fibers improves thermal stability, thermal conductivity, mechanical properties, wearability, and IR emissivity of the composite fibers. For example, with only ~ 0.2 wt% loading of GO, a ~50% improvement of tensile strength and 25% enhancement of Young's modulus were obtained [143, 145]. In a recent study, lead-free and radiation-resistant composite fiber was spun via a pilot-scale wet spinning process incorporating submicron-sized inorganic $BaSO_4$ particles as X-ray absorption fillers into the viscose spinning solution. Even after being washed 20 times, the composite fibers maintained good mechanical qualities and durable washing resistance. As a result, these fibers and fabrics can be used as the foundation for X-ray radiation-resistant lightweight clothing and detective surgical yarn [144]. Besides inorganic fillers, different bionanoparticles (cellulose nanocrystals, lignin, and chitin nanocrystals) can also be used as reinforcements to improve the chemical and thermo-mechanical performance of RC matrix [146, 147].

5.2 RC Composite Film/Membrane

5.2.1 RC/Graphene Composite Film

Graphene oxide (GO) synthesized from graphene nanosheets is a quasi-two-dimensional (2D) honeycomb lattice material with large oxygen-containing functional groups (hydroxyl, epoxide, carbonyl, and carboxyl) on its basal planes and edges. These chemical functional groups make GO very hydrophilic, promoting full exfoliation and homogenous dispersion of GO in the polar polymer matrix and considerably improving interfacial interaction [148–150]. Furthermore, cellulose has a strong interaction with graphene, for which graphene/cellulose nanocomposite films exhibit a significant improvement in the electrical conductivity, mechanical and thermal properties [151–153]. However, due to the strong π–π stacking interaction between graphene sheets, surfactants or stabilizers are needed to prevent the re-stacking of graphene sheets in ILs and the matrix. Obtaining uniformly dispersed graphene sheets in ILs without additives continues to be a challenge [154]. Interestingly, thermally reduced GO and ILs-reduced GO (IRGO) can be stably dispersed in IL for up to several months without the help of any additional stabilizers. And homogeneous dispersion of IRGO sheets throughout the cellulose matrices can enhance the mechanical performance of the regenerated nanocomposites films transferring the load from cellulose matrices to IRGO sheets [150, 155]. However, the RC composite film still shows insufficient water resistance because of the abundant hydrophilic hydroxyl groups in cellulose molecular chains, which restrict its packaging application for water-sensitive food and drugs [156, 157]. Incorporating layered nanofillers with a high aspect ratio into polymers can result in high-barrier nanocomposite films, where the layered nanofillers are expected to act as an impermeable barrier and force a tortuous pathway for gas molecule diffusion, significantly improving the barrier performance of nanocomposite films [158–160]. Furthermore, lipophilic modification (grafting with long alkyl chains, e.g., octadecylamine or dodecylamine) of the GO surface can facilitate uniform dispersion in the polymer matrix and improve hydrophobicity. In a recent work, an impermeable and hydrophobic GO modified by chemically grafting octadecylamine (GO ODA) has been utilized to enhance the water vapor barrier performance of RC nanocomposite films (Fig. 8). By adding just 2.0% wt percent of GO-ODA, the coefficient of water vapor permeability (PH_2O) was reduced by more than 20% compared to the pristine RC film [150].

5.2.2 Composite RC Films with Carbon Nanotubes

Carbon nanotubes (CNTs), chemically bonded with sp^2 bonds, have unique electrical, mechanical, and thermal properties. They have been extensively applied as reinforcing agents in polymers for the past 10 years, resulting in a wide range of possible uses in electrical devices, fuel cells, and sensors. They can be single-walled with a diameter of less than 1 nm (nm) or multiwalled with diameters greater than

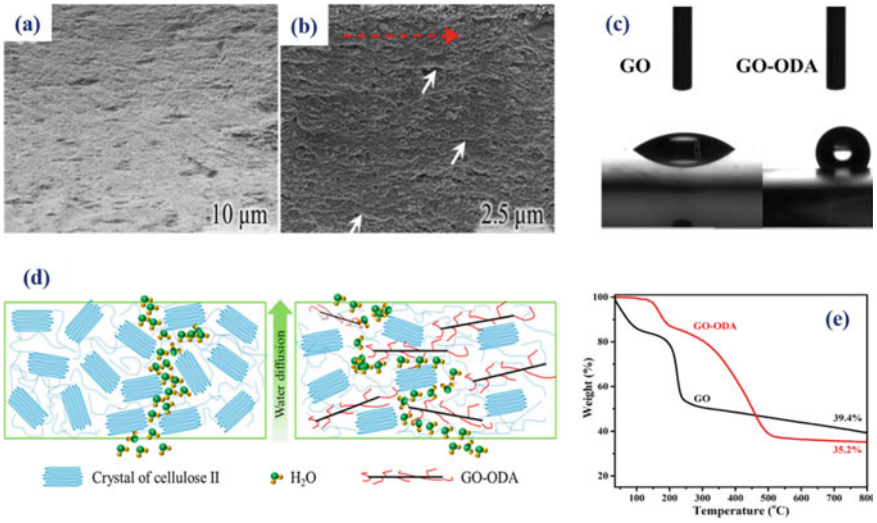

Fig. 8 **a** and **b** GO-ODA (as indicated by the red arrow) is inclined parallel with the RC film surface, labeled by the white arrow. Such orientation architecture of GO-ODA enhances the barrier performance of the RC/GO-ODA film. **c** GO exhibits a low WCA of 38.2° because of the abundant oxygen-containing functional groups. In contrast, the WCA of GO-ODA reaches 125.8°. **d** Schematic diagram of water vapor diffusion in neat RC (left) and RC/GO-ODA nanocomposite films (right). The addition of hydrophobic GO-ODA results in low water vapor permeability by disrupting hydrogen bonding between GO and H_2O, creating a tortuous path for diffusion and lowering the diffusion rate. **e** GO-ODA exhibits high thermal stability and antipyrolysis (the weight loss is nearly zero) below 120 °C. Republished with permission from [150].

100 nm. Carbon nanotubes could be nanodispersed into the cellulose matrix because cellulose has extraordinarily strong interaction with carbon nanotubes. Fabrication of multifunctional CNT-integrated RC composite film, which combines the superior mechanical, thermal, and electrical properties of CNTs and the biocompatibility of cellulose, is of great interest to polymeric science [151–153]. However, the efficient dispersion of CNTs in the cellulose matrix is a major challenge. Among different solvents, NaOH/urea aqueous solvent is the more common and cheaper, which not only dissolves the native cellulose but also disperses CNTs into the RC materials for smart functionalization [161].

Recently, a flexible and stretchable artificial electronic skin (E-skin) has been prepared from (RC)-CNT composite films dissolving cellulose in NaOH/urea aqueous solution in the presence of CNT, casting, and then regenerating in 5% sulfuric acid. A silk microstructure was pressed onto the surface of RC-CNT composite films. The RC-CNT composite film possessed favorable sensing performance in addition to its good flexibility, high tensile strength (61.6 MPa), and strain (17.7%) with no cytotoxicity [162]. But a much higher content of CNTs in the composite is necessary to improve its electrical conductivity. Unfortunately, when the CNT content is

increased, the composites experience dramatic decreases in their mechanical properties, arising from the unavoidable aggregation of CNTs. Furthermore, the exposure of CNTs on the surface of bulk nanocomposites is undesirable for some applications as it compromises personal safety. In this consequence, incorporating a robust enhancer with strong interfacial adhesion between the CNTs and the cellulose layers improves the mechanical performance of the hybrid system. For example, polyethylene oxide (PEO) has been incorporated with CNTs/cellulose composite films as a robust enhancer. The addition of PEO prevents deterioration of the mechanical properties of the material. Therefore, the composite film exhibits exceptionally high electrical conductivity of 20 S cm^{-1} with the addition of high content of CNTs with trace amounts of PEO. Furthermore, the film thickness and number of conducting layers also influence the EMI shielding performance indicating tunable EMI shielding efficiency (SE) for this composite. For instance, increasing the total thickness of composite may lead to ultrahigh SE exceeding 65 dB [140].

5.2.3 Composite RC Films with Energy Storage Capabilities

Preparing regenerated cellulose-based dielectrics with high energy storage capacity is complex, and reports on such materials are sparse. A continuous conductive network of metallic conductors or semiconductor particles in the RC matrix significantly improves the electrical and dielectric characteristics of the composite film. The electrical conductivity of RC-PPy composites produced in the presence of an oxidant with 12 wt% of PPy was 3.2×10^{-5}S/cm, which is approximately sevenfold higher than that of RC. However, high dielectric loss restricts their practical application as energy storage materials [163]. At this juncture, boron nitride nanosheets (BNNSs) have been incorporated with RC composite for dielectric energy storage materials, which are thermally conducting and electrically insulating. The RC-BN nanocomposite film with a 2D layered-structure displays outstanding dielectric properties, thermal conductivity, and mechanical properties. Here, cellulose molecules serve as a stabilizer for exfoliated BNNSs and provide the nanocomposite with a high dielectric constant while BNSS significantly improves their breakdown voltage. Surprisingly, 10 wt % of BNNS in the nanocomposite leads to a film with an energy storage density of 4.1 J cm^{-3} and a breakdown voltage of 370 MV m^{-1}. The energy storage density is significantly superior to any commercial dielectric polymer (poly vinylidene fluoride and biaxially oriented polypropylene) or biomass-based material discussed in the literature. The dramatic enhancement in the thermal conductive property results from an excellent in-plane thermal conductive property of BNNS together with forming a 2D-layered structure in the composite, in which a large contact area between BNNSs minimizes the interfacial thermal RC resistance when heat transfers along with the BN film [164].

5.2.4 Composite Semiconductor Oxide Thin Films

The oxide semiconductors, such as TiO_2, ZnO, Cu_2O, Bi_2WO_6, and BiOX (X = Cl, Br, I), have been widely used in the field of photocatalysis to produce organic–inorganic hybrid material. The hydroxyl groups of cellulose can coordinate effectively with metal cations of semiconductor oxide and allow the particles to be scattered in cellulose equally. Therefore, incorporating semiconductor oxide particles into the cellulose polymer matrix can improve the characteristics of nanocomposites [165, 166]. Table 5 represents some recent works on RC-based semiconductor oxide thin composite film. In a recent study, a green organic/inorganic hybrid membrane having both adsorptive and photocatalytic capacity was fabricated from recycled newspapers via the phase inversion method. Figure 9c–e revealed the well dispersion of TiO_2 nanorods on the surface of the RC/TiO_2 nanocomposite membranes. Additionally, the presence of N-doped anatase/rutile mixed phase TiO_2 nanorods in the RC membrane matrix improved the morphological and physicochemical properties of the composite. A strong hydrogen bonding interaction prevailed between the hydroxyl groups of RC and the TiO_2 nanorods (Fig. 9a). Conversely, nitrogen as a dopant in the TiO_2 lattice structure supported the highly visible light absorption capabilities of the produced RC/TiO_2 nanocomposite membrane. Under UV and visible light irradiation, the resulting membranes demonstrated considerable photocatalytic efficacy in degrading phenol in the aqueous phase. The degradation mechanism of phenol is depicted in Fig. 9b. RC membrane with 0.5 wt% of TiO_2 nanorods exhibited high adsorption capability compared to the others due to having the highest porosity and mean pore size because of TiO_2 nanorods incorporation (Fig. 9i). However, high loading of TiO_2 leads to the aggregation of nanoparticles and blocks the pores of the membrane, and reduces the porosity (Fig. 9f–h) [167].

6 RC-Clay Composite Film

Nanoclays (montmorillonite, halloysite, MXene) are nanosized silicate particles with nanopores with several enhancement properties. They have become very popular as reinforcing fillers for composites among the various nanoparticles due to their high aspect ratio, potential exfoliation characteristics, and superior mechanical performance [168]. Additionally, nanoclays are well dispersed in the RC matrix. They have strong interactions by forming hydrogen bonding between the silanol or siloxane groups on the clay surface and the hydroxyls of RC. Such strong interactions are verified by the significant improvement of the mechanical and thermal properties and can promote excellent nanoreinforcement for polymer nanocomposites and improvements in the film properties. RC/clay nanocomposite film exhibits improved optical transparency, oxygen barrier properties (reduced permeability), water resistance, and EMI shielding properties [139, 169, 170]. Recently, a flexible delaminated 2D composite film with EMI shielding properties has been fabricated via a facile vacuum filtration method by continuously depositing MXene (d-$Ti_3C_2T_x$) flake on the surface

Table 5 Recent studies on the RC-based semiconductor oxide thin composite film

Composite film	Dissolution solvent	Improved performance	Potential application	Refs.
Nano-ZnO/RC	NaOH/urea aqueous solution	Photocatalytic degradation efficiency	Degrading organic dye wastewater	[186]
RC/N-TiO_2 nanocomposite	NaOH/urea aqueous solution	Photocatalytic activity without suspension in the water	Water and wastewater treatment application	[187]
Regenerated cellulose/ZnONP nanocomposite	LiCl/DMAc	Semitransparent, antimicrobial properties, UV and oxygen barrier properties, thermal stability, and crystallinity	Food packaging	[188]
BiOBr/RC composite	LiOH/urea aqueous solution	Photocatalytic activity, stability under visible light irradiation at room temperature	Photodegradation of organic pollutants	[166]
Regenerated cellulose-ZnO hybrid film	LiCl/DMAc	Flexibility	Strain sensors, biomedical sensors, flexible display devices, and optoelectronics	[189]
Regenerated bacterial cellulose-ZnO nanocomposite	NMMO	Enhanced thermal, mechanical and biological (antibacterial) properties	Biomedical applications (bioelectric analysis)	[190]
Regenerated cellulose/N-doped TiO_2 nanocomposite membrane	NaOH/urea aqueous solution	Photocatalytic performance	Portable photocatalyst in the field of wastewater treatment	[167]

of the r-CNFs film to form an overall electrically conductive network (Fig. 10a). The d-$Ti_3C_2T_x$ deposition on the r-CNFs film results in wrinkled surfaces because the r-CNFs film swells in water during filtration and shrinks during the drying (Fig. 10b and c). The increased conductivity and higher specific surface area of d-$Ti_3C_2T_x$ generate more conductive pathways for charge carriers, which is advantageous for EMI shielding. A part of the electromagnetic (EM) waves is reflected when the incident EM waves are exposed to the d-$Ti_3C_2T_x$/r-CNFs composite film, as shown in (Fig. 10e). The multilayer structure of the d-$Ti_3C_2T_x$ on the surface of the r-CNF film facilitates multiple internal reflections, and the EM waves can be reflected back

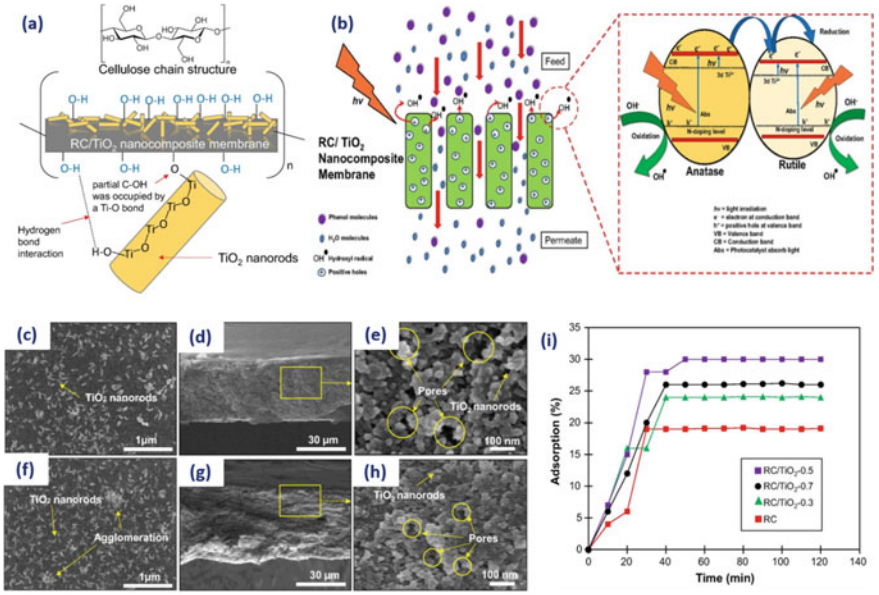

Fig. 9 **a** Interaction between –OH groups of RC and the TiO_2 particles in RC/TiO_2 nanocomposite membrane. **b** Degradation process of phenol with RC/TiO_2 nanocomposite membrane. Enlarge is the photocatalytic mechanism over the N-TiO_2 anatase TiO_2/rutile TiO_2 mixed phase. **c–e** FESEM images of RC/TiO_2-0.5, **d** and **e** show the cross-sectional view **f–h** RC/TiO_2-0.7, **g** and **h** show the cross-sectional view, and **i** phenol adsorption kinetics in the dark. Republished with permission from [167]

and forth between the layers, resulting in complete absorption and energy dissipation of the EM waves in the structure. In addition, the r-CNFs film with thicker d-$Ti_3C_2T_x$ coating absorbs more EM waves. Accordingly, the EMI SE is more excellent. The composite film (d-$Ti_3C_2T_x$/r-CNFs) with 15 mm thick d-$Ti_3C_2T_x$ coating demonstrated exceptional EMI SE (up to 42.7 dB) at the frequency of 2–18 GHz (Fig. 10f). Besides, the d-$Ti_3C_2T_x$/r-CNFs composite film exhibited high tensile strength and poor breaking elongation. The tensile strength of d-$Ti_3C_2T_x$/r-CNFs composite films increased from 16.8 cN to 29.1 cN with the thickness of the coated d-$Ti_3C_2T_x$ because of the large interfacial interactions between the 2D d-$Ti_3C_2T_x$ and the r-CNFs film which is formed by hydrogen bonding (Fig. 10d). The breaking elongation of composite films was lower than that of r-CNFs due to the stiffening of the structure after filtrating d-$Ti_3C_2T_x$ solution [171].

6.1 All Cellulose Composite Film

The earliest all-cellulose composites were developed of ramie fibers embedded in a matrix of RC. They had outstanding mechanical and thermal properties due to the

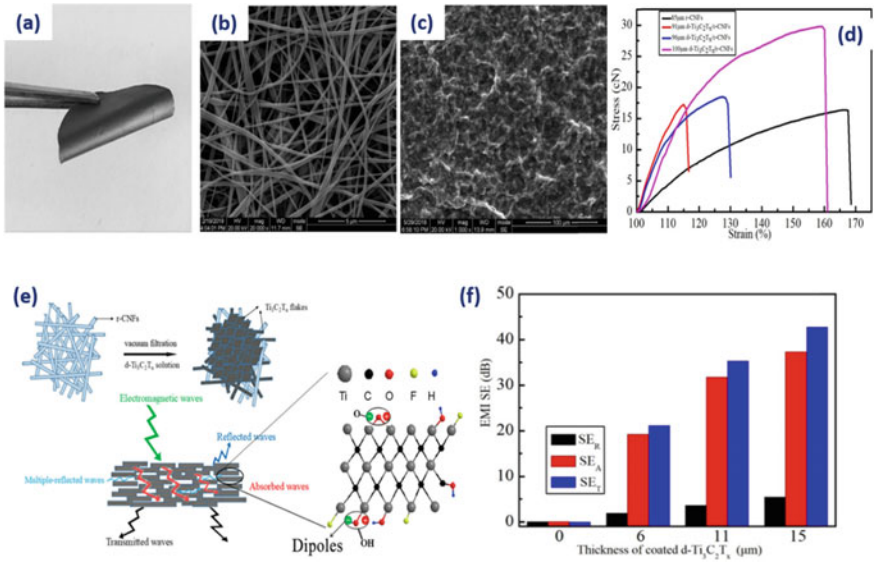

Fig. 10 **a** d-$Ti_3C_2T_x$/r-CNFs composite film, **b** SEM image of r-CNFs film, **c** SEM images of d-$Ti_3C_2T_x$/r-CNFs composite film, **d** stress–strain curves of r-CNFs and d-$Ti_3C_2T_x$/r-CNFs composite films at a different thickness, **e** EMI shielding mechanism of d-$Ti_3C_2T_x$ /r-CNFs composite, **f** average values of EMI SE of r-CNFs and d-$Ti_3C_2T_x$/r-CNFs films at a different thickness of d-$Ti_3C_2T_x$ coating, respectively. Republished with permission from [171]

exceptional compatibility between the cellulose reinforcement and matrix. Subsequently, numerous all-cellulose composites have been proposed to develop innovative materials with the key characteristics of being biobased and biodegradable [91, 172]. Several all-cellulose composites have been developed by either partially dissolving cellulose fibers or directly integrating cellulose nanocrystals (CNCs) into a cellulose matrix [173]. However, the length/diameter ratios of CNCs are low, and their production processes often involve concentrated acid or other harmful chemicals. Recently, native cellulose nanofibrils (CNFs) have been successfully utilized as reinforcing fillers due to their unique characteristics such as large length/diameter ratio, high mechanical properties, and the ability to form highly porous meshes [174].

6.2 RC-Based Composite Bead/Microstructure

Regenerated cellulose-based composite beads with different diameters ranging from micrometer to millimeter can be used in many advanced applications. They can be fabricated by introducing chemical functionalities or blending with organic and inorganic compounds [175]. Over the last decades, various methods for fabricating beads or microspheres have been developed, including emulsification, dispersion,

and spray drying. These approaches have drawbacks, such as a lack of control over shape and size distribution, and some are hazardous to the environment. The electrostatic technique is one of the most convenient and continuous methods for the controllable production of small particles or fibers with uniform and desirable size, which is critical for fabricating microspheres or fibers in the biomedical field. It is based on the balance between an electrostatic force and the solution surface tension [176]. Recently, nanoporous regenerated cellulose/soy protein isolate (SPI) composite beads with good thermal stability and cytocompatibility have been fabricated by high-voltage electrostatic technique in the presence of coagulant (sulfuric acid). Changes in fabrication parameters such as high voltage and SPI content can control the size of the beads [177].

6.3 RC-Based Composite Hydrogel and Aerogel

RC-based composite hydrogels have drawn large-scale research attention worldwide and have captured a potential platform in biomedical engineering and interactive devices. The presence of RC in hydrogel dramatically enhances the water holding capacity, texture, and mechanical properties of the composite [97, 178]. Furthermore, the mechanical properties of the composite gel can be modulated by incorporating a small amount of GO which has a strong hydrogen–bond interaction with RC molecules. For example, a novel ternary hydrogel was synthesized by repeated freezing and thawing in NaOH/urea aqueous solution incorporating GO with RC and polyvinyl alcohol (PVA). Synthesized ternary hydrogel exhibits enhanced mechanical properties relative to RC/PVA hydrogels. More importantly, the presence of the carbonyl groups enables GO to impart excellent pH sensitivity to the synthesized hydrogel [97]. In addition, GO incorporated 3D crosslinked RC composite aerogel shows increased dye adsorption capacity due to the unique graphitized planar structure, extremely high specific surface area, and π-π conjugation of GO. For example, with the addition of only 0.5 wt% GO methylene blue adsorption efficiency of RC/GO aerogel reached 99.0% by electrostatic interactions. Besides, the excellent reusability and thermal stability of composite aerogel make this a suitable candidate for removing toxic compounds in environmental engineering [179].

6.4 RC Nanocomposite Materials

Cellulose nanocomposites containing dispersed functional inorganic nanoparticles have gained substantial research focus in material sciences due to their potential applications in catalysis, electronics, sensors, nanocomposites, drug delivery, wastewaters treatment, and functional food packaging. Emulsion polymerization, grafting/covalent conjugation, and one-pot synthesis/hydrothermal processes are used to synthesize RC-based nanocomposite materials [180–182]. Among different

synthesis routes, one-pot synthesis is the simplest one where hybrid nanomaterials can be prepared during the regeneration of cellulose. Recently, antimicrobial hybrid nanomaterials have been prepared by one-pot syntheses of silver, copper oxide, or zinc oxide nanoparticles during the regeneration of cellulose from cotton linter and microcrystalline cellulose. The metallic nanoparticles are linked to the cellulose via interacting with the hydroxyl group of the cellulose, and the synthesized RC/metallic NPs hybrids showed strong antibacterial activity with thermal stability [180].

7 Conclusions and Future Outlook

Reducing the overreliance on petroleum-based resources is an essential prerequisite to building a pollution-free and sustainable world. Due to the inherent advantages of safety, biocompatibility, and biodegradability, cellulose has become a great choice for supplanting petroleum-based products to grow into new applications without polluting the environment. Furthermore, the environment-friendly physical dissolution and regeneration process has brought about a green revolution in the comprehensive utilization of cellulose-like natural resources since it avoids the consumption of chemicals, and most of the agents can be recycled and reused, retaining nature of cellulose. Furthermore, the abundance of –OH groups provides cellulose with an attraction for inorganic/organic compounds, allowing for the creation of hybrid materials broadening the scope of cellulose's possible applicability as a functional material. This review has attempted to provide a vision of the greener approaches to cellulose dissolution and regeneration. In addition, it covers some important aspects of different shapes of regenerated cellulose-based materials and composites, such as their mechanism of synthesis, essential properties, and potential applications. Overall, an explanation of recent innovations in regenerated cellulosic materials with their potential applications, their material processing technologies, process parameters, the resultant properties, and functions reported in this chapter may expand the thought about the current trend of exploring regenerated cellulosic materials with novel strategies. Additionally, this work will provide an overview to mitigate the current weaknesses and pave the way for versatile functionality for next-generation applications. To conclude, the following scopes are recommended for further research consideration based on the limitations in the literature reviewed.

– Fiber regenerated from bacterial cellulose through the lyocell process is an environment-friendly approach. However, the mechanical robustness of regenerated fibers should be ensured with substantial study [73].
– As a sustainable approach, closed loop recycling has gained a growing research interest. However, the purification of the waste garments before processing is barely explained in the literature, which is a crucial aspect of material synthesis. Additionally, extensive research is required to delineate the molecular properties of the pulp reclaimed from cotton waste garments before regeneration into new fibers [21, 70].

- The development of modified films and membranes having better stability under wet and dry conditions, controlled porosity, and a distinct pore size distribution is an excellent scope for further exploration. Another area of study might be the prevention of shrinkage during drying and the introduction of greater flexibility to enable use as a transparent film [2, 43].
- Most of the research works covered in this chapter deal with lab-based synthesis and applications. Therefore, future work can be directed to explore the bulk processability and performance of materials of different shapes in real application areas. The primary attempt could be the pilot-scale production and application mimicking the actual situation.
- In a nutshell, careful investigation and systematic nanoengineering of regenerated cellulose-based composite could aid us in achieving their better sustainability and performance, thus may broaden the possible applications of regenerated cellulose.

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Surface Modification of Regenerative Cellulose (RC) for Biomedical Applications

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Abstract In modern green and sustainable chemistry, regenerative cellulose (RC) plays an increasingly critical role in science and engineering, including electronics and biomedical applications such as tissue engineering, drug delivery, and biosensing with its high biocompatibility and biodegradability, less toxicity, and high mechanical strength. RC can be surface modified through hydroxyl groups using ligands, polymers, metal nanoparticles, and carbon-based nanomaterials to highly chemical active and sophisticated materials for various biomedical applications. The surface-modified RC confers excellent chemical, electrical, optical, and mechanical properties that can selectively bind to the target biomolecules and cellular environments easily. This chapter reviews RC surface modification methods by using organic and inorganic nanomaterials for biomedical applications. Furthermore, this review summarizes the recent advances in adopting polymers and inorganic materials capable of functionalizing the RC surfaces and the effects of the guest molecule—RC composites in tissue engineering, biosensing, and wound dressing applications.

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This review aims to provide a comprehensive overview of the consistent improvement of functionalized RC and RC composites for highly sophisticated biomedical applications.

1 Introduction

Cellulose is the most abundant natural polysaccharide that can be extracted from plants and microbes such as bacteria and algae. Linear polymer chain molecular structure, high mechanical strength, high chemical and thermal stability, biodegradability, abundant functional groups that can be modified as favorable chemical structures and readily modified by a wide range of chemicals make cellulose a highly potential material for a wide range of scientific applications including biomedical applications such as wound dressing, drug delivery, anti-bacterial membrane, and biosensing matrix [1, 2]. However, native cellulose derived from wood pulp or microorganisms is challenging to process or modify into any favorable material due to its high crystallinity and insolubility in many non-toxic green solvents. Therefore, to produce cellulose as soluble material with reduced crystallinity, the cellulose regenerative process has to be carried out by powerful solvent treatment [3]. During the cellulose regenerative process, the supermolecular structure of cellulose is collapsed and rearranged and finally regenerative cellulose (RC) derivative can be produced. These RC derivatives can be readily dissolved in a wide range of solvents. By definition, RC has a structural transformation from cellulose I (native cellulose) to cellulose II (regenerative cellulose) by eighter derivatizing and non-derivatizing processes. During this structural transformation, the disorder occurs mainly in the hydrogen-bonded intermolecular region of RC molecules and monomolecular RC sheet that formed by stacking glucopyranoside planes by van der Waals forces. This transformation results in antiparallel chain packing in RC [4]. However, regenerated cellulose's chemical and mechanical properties depend on the solvent and coagulant used in the cellulose regeneration process.

Regenerative cellulose is a 2D structural nanofabricated product. RC has numerous advantages, including flexibility, high thermal stability, ease of the process, and abundant oxygen-containing groups that allow various biomolecules, polymers, and nanoparticles (NPs) to be conjugated [5–7]. These nanomaterials and functional polymer crosslinked, grafted, and surface-modified RC supports the development of novel nanocomposites that exhibit optimum properties in biomedical, electronic, and energy applications [8, 9]. Furthermore, high solubility in a wide range of organic solvents and aqueous ionic solvents confer great opportunity to produce RC-based nanofiber, thin films, aerogels, and hydrogel matrices that can be effectively utilized in a wide range of biomedical applications [10, 11]. For instance, RC polymer and RC composites dissolved in ionic or derivatizing solvents can be easily processed as nanofiber via the electrospinning method [11, 12]. These electrospinning nanofibers possess large surface area and porosity that can be effectively utilized in biosensors, drug delivery, wound dressing, tissue engineering scaffolds, and multiple

nanocoating applications. Besides, RC-based 3D nanostructures such as aerogels and hydrogels with more nanopores can be easily processed by solvent casting followed by lyophilization techniques [13]. Highly biocompatibility, biodegradability, large surface area, low density, and higher oxygen and ion permeability of these hydrogels and aerogels are increasingly used in various medical fields such as infection control, wound healing, surgical implantation, and drug delivery [13, 14].

Recent advances in RC-based nanomaterial composites show numerous merits in biological and biomedical applications such as biofouling, antimicrobial coating, wound dressing, and tissue engineering. Notably, recent advances inorganic nanoparticles incorporated RC composite materials exhibit novel functional properties that minimize the limitation of RC alone. For instance, metal nanoparticles or graphene material incorporated in RC membrane exhibit higher conductivity and less toxicity, making them ideal for long-term implantable biosensors [15]. Besides, antimicrobial nanoparticles (NPs) such as Ag NPs, CuO NPs, and ZnO NPs dopped RC composite thin films and coatings effectively prevent the growth of microbes and biofouling for long-term applications. Nobel metal NPs such as Au NPs incorporated in RC composite could be used as a potential drug delivery system in wound healing and biosensor applications [16]. Abundant oxygen groups of RC or chemically surface modify RC materials effectively affine with these NPs via ionic charge interactions and ease the controlled release of NPs in drug delivery applications. In addition, without any complicated process steps, NPs incorporated RC composite architectures can be easily produced by electrospinning, dip coating, and other casting methods by simply mixing NPs into RC precursor solutions. In this context, RC opens a new promising path to produce novel, enticing nanocomposites with desired and tenable properties that could be effectively utilized in biomedical applications. Therefore, this chapter highlights the recent advances in RC by highlighting the RC properties, manufacturing method, and molecular mechanism of nanoparticle incorporated RC composites and their potential applications in the biomedical field.

2 Overview of Cellulose Chemical Modification of Regenerative Cellulose

All kind of cellulosic polymer is made by anhydrous repeating D-glucose units linked via $\beta(1 \rightarrow 4)$ bonds. In regenerated cellulose, these polymer chains are arranged from highly ordered crystalline domains to disordered nanocrystalline domains and form cellulose fibrils [17, 18]. These polymer molecules are arranged layer by layer as stacks in cellulose fibrils to construct a crystalline structure. Rich hydrogen bonds are formed between the adjacent monomer hydroxyl groups in each polymeric unit. At stake, polymer molecules are linked by intra hydrogen bonds and Van der Waal forces. In regenerated cellulose, only one hydrogen bond is formed between two monomeric units in a chain, whereas two hydrogen bonds link two monomeric units in native cellulose [3]. In addition, in regenerated cellulose, each

molecule pairs hydrogen bonds between the side-by-side polymer chain and the adjacent polymer chain, whereas native cellulose only pairs hydrogen bonds between adjacent molecules. Regenerated cellulose monomer units are linked by O2H—O2' intermolecular hydrogen bonding and O2H—O6' intramolecular hydrogen bonding, while native cellulose link at O3H—O5' intermolecular hydrogen bonding and O6H—O3' intramolecular hydrogen bonding. As a result, regenerated cellulose results in a low degree of polymerization and reduced crystallinity, which increases the solubility of regenerated cellulose in a wide range of solvents. This allows regenerated cellulose to be modified with various surface modifications [17].

Regenerated celluloses are abundant in hydroxyl groups that can make hydrogen bonds with H_2O molecules and aid in absorbing a high amount of moisture [18, 19]. This moisture absorption property of regenerated cellulose has been efficiently utilized in wound dressing and moisture absorbing bio coating applications. Furthermore, these hydroxyl groups are the major reactive groups in regenerated cellulose. Therefore, as shown in Fig. 1, different moieties can be introduced to regenerated cellulose via the chemical modification of these hydroxyl groups [18]. Generally, oxidation of the hydroxyl groups of cellulose is the most common method to introduce aldehyde, carboxylic, and amino functional groups to the regenerative nanocellulose fibers. These functional groups are chemically reactive and can be further applied for grafting and crosslinking other polymers to the cellulose molecules. One of the easiest ways for oxidized the regenerated cellulose molecules is by deriving the carboxylic group on the carbon atom of an anhydrous glucose unit by nucleophilic displacement reaction [20]. In these reactions, deoxy cellulose derivatives can be obtained. The TEMPO (2,2,6,6-Tetramethylpiperidinyloxy or 2,2,6,6-Tetramethylpiperidine 1-oxyl) oxidation reaction is generally used to introduce the carboxylic group to the anhydrous glucose units. Apart from these reactions, periodate-based oxidations are used to obtain dialdehyde cellulose (DAC) [18, 20]. In this reaction, periodate components break and open the C2, and C3 bonds at the anhydrous glucose unit and form dialdehyde groups that are further oxidized as carboxylic or hydroxylamine groups. These oxidized regenerated cellulose derivatives can be used to graft with other functional polymers via covalent bonds or electrostatic interactions and form biocomposite structures. In addition, regenerated cellulose modification by alkali treatment, silanization, acetylation, etherification, graft copolymerization, benzoylation, and isocyanate treatment are used to functionalize the surface of regenerated cellulose nanofibers. These modifications confer preferable hydrophobic/hydrophilic properties, surface charges, biocompatibility, and the ability to conjugate with biomolecules [18].

Another potential chemical modification of regenerated cellulose is crystalline nanocellulose (CNC). Crystalline nanocellulose is synthesized from regenerated cellulose via acid hydrolysis followed by mechanical disintegration or direct solvent dissolution of CNC particles in ionic liquids [21, 22]. This CNC derived from regenerated cellulose also can be used in a wide range of biomedical applications such as drug delivery, biosensing, and biomembrane applications [23]. Besides, surface modifications have been widely studied by inorganic nanomaterials such as graphene,

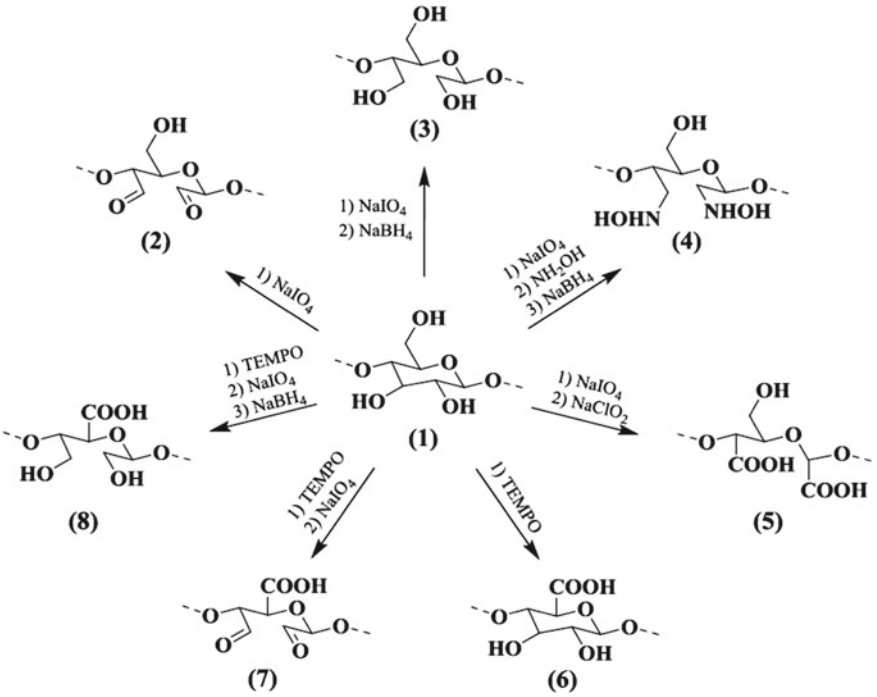

Fig. 1 Schematic description of the different routes chosen for chemical modification of cellulose fibers. *Republished with permission from* [18]

graphene oxide, carbon nanotubes, and metallic nanoparticles. Generally, these inorganic nanomaterials interact with chemically modified regenerated cellulose derivatives such as oxidized regenerated cellulose via electrostatic interaction. The nanomaterials' surface-functionalized regenerated cellulose exhibits antibacterial properties, high thermal stability, mechanical strength, and electrical conductivity.

3 Morphological Properties of RC-Based Materials for Biomedical Applications

RC is a favorable material to be modified in various morphological forms such as nanofibers, nanofibrils, sponges, hydrogels, and membranes. Notably, the nanofibril structure of regenerative cellulose, such as regenerative BC, allows it to easily produce nanobeads without any capping agents or ligands [24, 25]. Drugs, peptides, and DNA molecules are decorated on the RC beads and applied for drug delivery. The higher surface area of nanometric size and higher porosity of these nanobeads aid in carrying a higher number of drugs or biomolecules to the target [26]. In addition, low degradability rate, less solubility, and high resistivity of pH changes of RC nanobeads

prolong the drug delivery rate [27]. Besides, longer polymer chains and the ability to dissolve in derivative solvents and ionic solutions confer great opportunity to produce RC-based nanofibers widely studied for tissue engineering scaffold fabrications and antimicrobial films. Notably, RC electrospun nanofiber has been studied for a wide range of tissue engineering scaffolds such as neuronal tissue scaffolds, nerve conduits, and cartilage scaffold applications. High mechanical strength, resistance to body physiochemical changes, less immunological response, and low degradability rate properties of RC comply with rigid tissue scaffolds such as cartilage tissue scaffolds [28]. Similarly, less toxicity, high biocompatibility, similar to the topographical structure and high surface area, and a high number of functional groups of RC nanofiber nerve conduits and scaffolds have shown improved results in soft tissue regeneration, such as neural tissues [29]. In addition, the electrospinning technique can produce an RC nanofiber with different topographical orientations or patterns, which could be used to guide the neurons. Furthermore, RC membrane, gauze, and thin film with high porosity can be synthesized via electrospun, solvent leaching, or lyophilization techniques. Higher surface area resulting from high porosity of RC membranes and abundant –OH groups facilitate the high oxygen permeability and moisture absorption, which are the ideal properties of wound dressing applications. Along with these favorable properties, antimicrobial drugs, antimicrobial metallic ions such as Ag^{+}, Cu^{2+}, and Zn^{2+} and antimicrobial nanoparticles such as Ag^{2+}, Au^{+}, Zn^{2+}, and Cu^{2+} loaded RC films have exhibited enhance antibacterial properties [30].

4 Regenerated Cellulose Nanoparticle Composite for Biomedical Applications

Producing a highly biocompatible, safe, and durable biopolymer matrix has become crucial in biomedical applications. Regenerated cellulose thin films, nanofibers, aerogels, and hydrogels gain considerable attention due to their high mechanical strength, flexibility, water absorption ability, high porosity, and large surface area [31, 32]. Large oxygen-containing groups and the ability to form nanofabricated structures make RC an ideal candidate for incorporating various active nanomaterials and producing biofilms. Generally, nanoparticles (NPs) can be attached to RC molecules via two mechanisms which are (1) higher surface charges of nanoparticles or ± surface charges of capping molecules may link with RC molecules via electrostatic interaction and (2) capping polymers of nanoparticles may crosslink or graft on the hydroxyl or functional groups of RC/RC derivatives [33]. Besides, as shown in Fig. 2, NPs incorporated in RC matrices can be produced by directly mixing NPs with polymer solution followed by the membrane processed methods such as electrospinning or solvent casting. In another ways, metallic salts can be reduced by the hydroxyl groups of RC, additional reducing agents such as $NaBH_4$ or hydrothermal process followed by the membrane process methods. In this context, metallic and inorganic nanoparticle-doped or conjugated RC nanostructures open

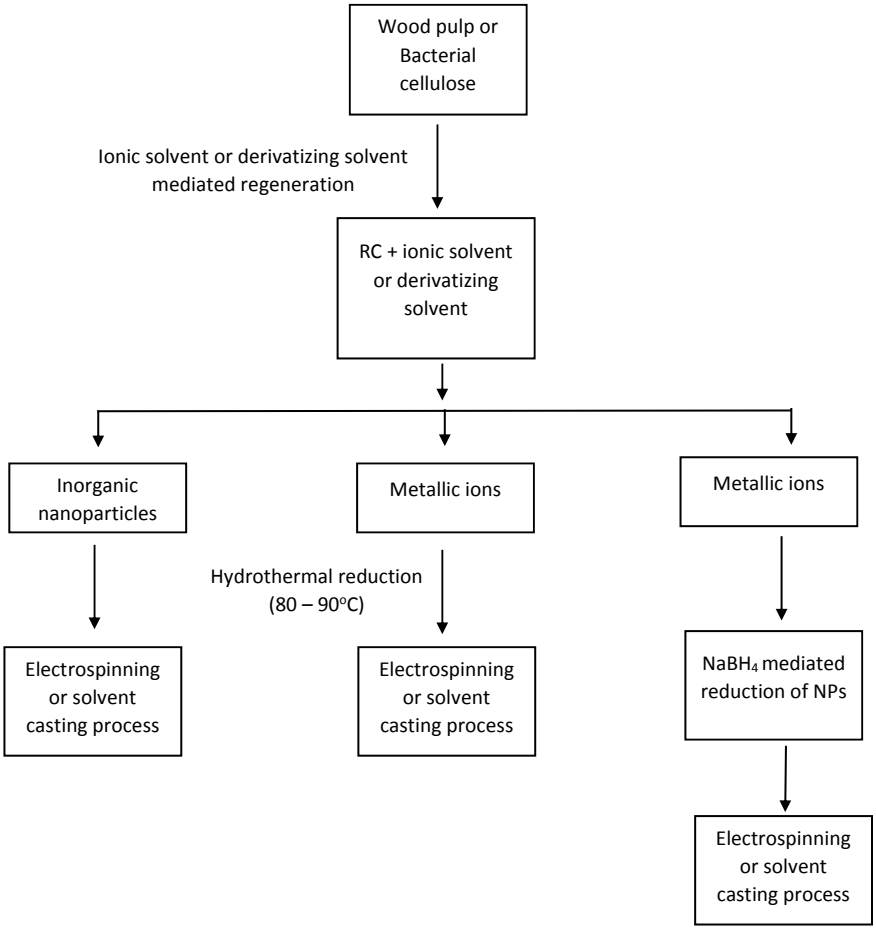

Fig. 2 Process steps for RC – NPs composite membrane synthesis

up new avenues to synthesize RC nanocomposites with unique properties such as hydrophobicity/hydrophilicity, antibacterial property, electromagnetic interference (EMI) shielding, and high ion/electron conductivity.

4.1 Antimicrobial RC-Nanoparticle Composites

Generally, antimicrobial RC nanocomposites are produced by doping antimicrobial metallic nanoparticles such as AgNPs and AuNPs and metallic oxide nanoparticles such as TiO_2, ZnO, and CuO NPs into the RC polymers [34, 35]. Metal and metallic oxide NPs doped RC composite are prepared in the form of thin film, nanofiber,

hydrogels, or sponges. Among these nanoarchitectures, RC – nanoparticle composite nanofibers gained considerable attention due to their high porosity and large surface area that facilitate the adsorption of microorganisms or controlled release delivery of active NPs. Notably, Ag NPs dopped RC nanofiber matrix has shown promising outcomes in wound dressing, food packaging, and dialysis membranes [33, 36, 37]. Electrospinning is a potential method to prepare AgNPs – RC nanofiber with a nanometric diameter and high porosity. To produce electrospun AgNPs – RC nanofibers, Ag NPs nanoparticles or $AgNO_3$ metallic salt is added to the RC polymer solution. Initially, RC is dissolved in ionic liquids such as N-methylmorpholine-N-oxide(NMMO)/water, 1-butyl-3-methylimizadolium chloride [BMIM]Cl/water, and sodium hydroxide (NaOH)/urea/water or derivatizing solvents such as dimethylsulfoxide (DMSO), dimethylformamide (DMF), fluoroacetic acid, formate acid, and triflouroacetic acid (TFA) [3, 38]. Ionic liquids-based solvent system degrades the cellulose chain via hydrolysis (alkaline) or making the hydrogen bond with RC molecules which further facilitates the ionic interaction of NPs with RC molecules.

On the other hand, derivatizing solvents cause intermediate reactions such as etherification reaction (for instance, in the presence of DMF), esterification reaction (in the presence of TFA) and form intermediate derivatives and reduce the crystallinity and dissolve RC molecules where NPs can be capped or conjugated with RC polymer chains [39]. Furthermore, these NPs-RC solutions are electrospun and produce nanofiber with optimum fiber diameter with high porosity. Herein, electrospun nanofiber diameter is manipulated by changing the electrospinning flowrate, applied voltage, conductivity of precursor solution (depending on the concentration of metallic NPs), and working distance (distance between nozzle and collector) [40]. Besides, high porosity in the nanofiber can be obtained by controlling the humidity and using low boiling solvents in precursor solution [40].

A previous study investigated the antibacterial property of Ag NPs dopped RC electrospun nanofiber [41]. In this study, Ag NPs (0.5, 1 and 2wt%) are added directly to the RC (6wt%) dissolved into the 1-butyl-3-methylimidazolium chloride ([BMIM]Cl) ionic solvent and electrospun via dry–wet electrospinning method. The fiber obtained showed higher wettability, lower thermal decomposition rate, and high tensile strength. These RC-Ag NPs composite showed high bioactivity and killed *E. coli* (Escherichia coli) almost entirely without any leaching [41]. In another way, Ag NPs- RC composite antibacterial films are prepared by directly reducing the Ag^+ ions by cellulose molecules. For instance, Ag-RC antibacterial film were prepared by directly reducing $AgNO_3$ to Ag NPs by RC molecules [30]. This study added silver nitrate into dissolved RC cellulose in N-methylmorpholine-N-oxide (NMMO) solvent and produced an antibacterial membrane via the solvent-casted method. In this facile method, $AgNO_3$ and cellulose molecules acted as an oxidizing and reducing agents, respectively. In higher temperature conditions (90 °C), a redox reaction occurs, and Ag NPs are formed, and nucleated AgNPs can be uniformly distributed in the solution, whereby a homogeneous Ag-RC membrane can be obtained. These AgNPs–RC membranes exhibited good antibacterial properties to *E. coli* and *S. aureus*. The significant advantage of this system is using RC as

the sole reducing agent. Using sole solvent offers a homogenous system that aids in uniformly reducing Ag^+ ions and dispersing AgNPs throughout the membrane.

Nevertheless, it is hard to control the size of NP as cellulose is a mild reducing agent. In these methods, cellulose-based architectures such as hydrogels are dispersed to the Ag^+ ion solution. In a heterogeneous environment, cellulose molecules can act as a capping agent, cover the AgNPs surface (adsorbed onto the AgNPs surface), and limit the antibacterial activity. Besides RC-AgNPs composite-based films and nanofiber, RC-based nanocomposite sponges are considered potential alternative gauze for wound dressing applications due to their high nano/micropore structure hydrogel property and mechanical strength. Ye et al. [30] fabricated RC – AgNPs composite sponge by dispersing the cellulose hydrogel into the Ag^+ solution, followed by the hydrothermal reduction of Ag^+ [30]. In this study, as shown in Fig. 3, RC was dissolved in NaOH/Urea solution in the presence of epichlorohydrin and RC hydrogel was prepared.

Further, RC hydrogel was dispersed into the AgNO3 aqueous solution at high temperatures, whereby Ag^+ was reduced by cellulose and AgNPs were formed. To obtain high porosity, AgNPs – RC was freeze-dried. This composite structure

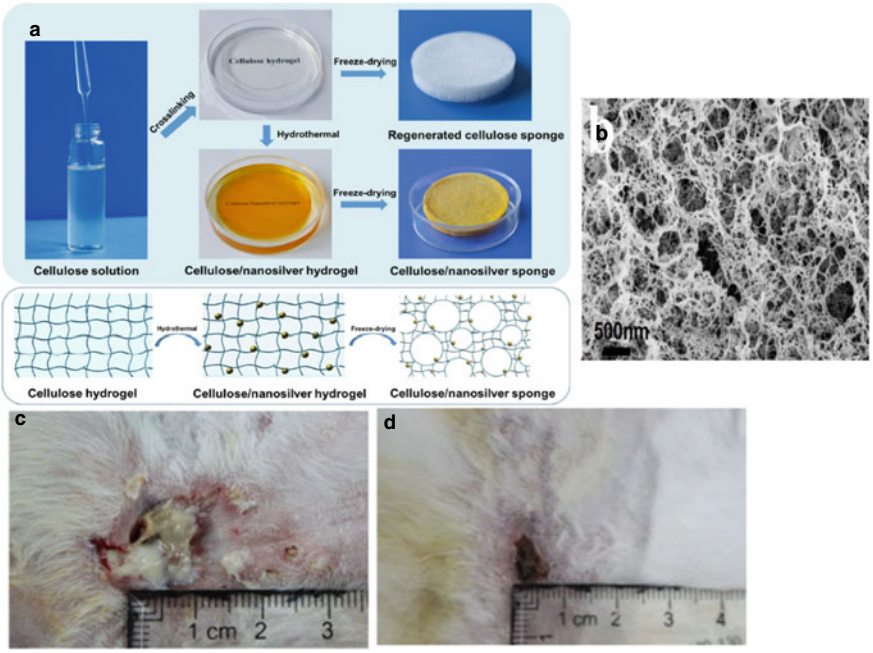

Fig. 3 Photographs of cellulose solution to the construction of regenerated cellulose sponge and cellulose/nanosilver composite sponges (top), and schematic architecture of the cellulose hydrogel and composite hydrogel and sponge (bottom). B. The SEM images of RCS-Ag, C. Visual observations of in vivo infected wounds healing process and the C. photographs of the wounds at 22 days are representative of C1. Bare RC group and C2. RC–Ag group (eight rabbits in each group). *Republished with permission from* [30]

exhibits excellent biocompatibility toward the high survival rate of 293 T cell lines. Furthermore, this sponge inhibits *E. coli* and gram-positive bacteria *S. aureus* in vitro study and efficiently healed the infected wounds in the rabbit model within 10 days, whereas infected conditions remain the same in the control model during the same period. However, compared to previous studies, this RC – AgNPs sponge lacks antibacterial activity [30]. This condition may be attributed to the agglomeration of AgNPs, heterogeneous diffusion and distribution of AgNPs into cellulose fibrils and RC act as a capping agent of AgNPs and cover the surface area. These consequences might have resulted from the heterogenesis AgNPs synthesis environment.

Similar to Ag NPs, copper (Cu) and zinc (Zn) NPs incorporated in RC composites also expressed efficient antimicrobial activity. ZnNPs and CuNPs dopped RC composite can be synthesized by directly adding the MNPs into RC solution followed by matrix preparation or metallic ion added into cellulose solution followed by redox reaction methods. For instance, a research group produced Ag, Cu, Zn NPs–RC/microcrystalline cellulose (MCC) composite by cellulose-based reduction of metal ion reaction and compared the antimicrobial activity of different MNPs – RC composite [36]. This study added 50 mM of silver nitrate, copper nitrate, or zinc nitrate solution to the regenerated cellulose and regenerated microcrystalline cellulose dissolved NaOH/urea solution at a higher temperature (80 °C) condition, and MNPs were formed. Eventually, these solutions were dried before obtaining RC-MNPs hybrid nanomaterial powder. Among these composites, compared to other RC-MNPs composites, RC – AgNPs and RMCC – AgNPs exhibit strong antimicrobial activity against *E. coli* and *L. monocytogenes* food-borne pathogens in a short time (6 and 9 h, respectively), whereas RC-CuONPs progressively inhibited the growth of bacteria and completely killed *E. coli* and L. monocytogenes (9 and 12 h). However, RC-ZnONPs only exhibited bacteriostatic activity against both *E. coli* and *L. monocytogenes* [36].

4.2 RC-Magnetic Nanoparticle (MNPs) Composites

Ferromagnetic nanoparticles dopped RC composites thin films also have potential biological applications such as separation, sensor applications, and smart biological devices [42]. Generally, magnetic nanoparticles—RC composites are synthesized by simply mixing ferromagnetic nanoparticles such as Fe_2O_3 into the RC solution, followed by the thin self-assembly, film casting, dip coating, or electrospinning methods. Alternatively, magnetic NPs–RC composites can be produced by electrospinning of RC solution followed by the impregnation of NPs into the electrospun nanofiber. In addition, magnetic nanoparticle loaded native cellulose or other cellulose derivatives thin films also can be treated by ionic liquids, and MNPs loaded RC nanofibers can be produced. For instance, RC—MNPs composite nanofiber film was produced by treating the magnetic iron oxide nanoparticles (MIONPs) loaded cellulose acetate (CA) using NaOH/urea to convert as RC-MINOPs composite [43]. This membrane showed zero magnetic remanence due to the efficient impregnation

of MINOPs, high surface area and high porosity of the RC membrane. Although MNPs incorporated RC composite has high potential in a wide range of biomedical applications, very limited studies have been done.

4.3 RC—Metal NPs for Biosensor Applications

Compared to native cellulose molecules, RC exhibits a highly flexible structure and high thermal stability due to its rearranged crystallinity. Along with these qualities, the high biocompatibility and low degradability rate of RC make RC material an ideal candidate for implantable and highly durable biosensor applications. Moreover, abundant hydroxyl functional groups of RC facilitate conjugating with a wide range of biomolecules such as enzymes, peptides, and nucleic acid that can be immobilized on cellulose to produce colourimetric, electrochemical, and SERS biosensors. Despite these advantages, the lack of electrical conductivity limits RC usage for electrochemical sensor applications. However, essential sensor properties such as electrical and optical properties such as localized surface plasmon resonance (LSPR), SERS, and optical transparency can be optimized by incorporating metallic and plasmonic nanoparticles such as Au NPs and Ag NPs and CNT. For instance, an RC membrane with SERS properties was produced by decorating it with Au NPs. In this study, (3-Aminopropyl) trimethoxysilane (APTMS) coated (positive surface charge) RC fiber was soaked into the AuNPs colloid before coating Au NPs [16]. This flexible composite showed excellent SERS sensitivity (10^{-9} M for Raman probe molecule, 4-Mercaptobenzoicacid (4-MBA)) and adsorption capability. Using the SERS mechanism, the flexible RC-Au NPs fiber mat was used to identify the dimetridazole (DMZ) from an aqueous solution. Furthermore, the flexible RC-Au NPs fibers swab was investigated to identify DMZ from the surface of fish by simply swabbing process (as shown in Fig. 4).

4.4 RC—Metal Nanoparticle Composite for Tissue Engineering Scaffold

Long term degradability, ability to carry and control release the drugs, high mechanical strength, high wettability, high porosity and ability to form fibrillated structure are the essential characteristics of hard tissues such as cartilage regenerated scaffolds. In this context, RC modified with metallic or inorganic nanoparticle composite could well satisfy these requirements. Herein, incorporated inorganic NPs can play a crucial role in drug encapsulation and delivery, improve the hydrophilic property of RC, and enhance thermal and mechanical strengths. Sofi et al. [44] produced the hydroxyapatite (HAp) and AgNPs immobilized RC scaffold for tissue engineering application

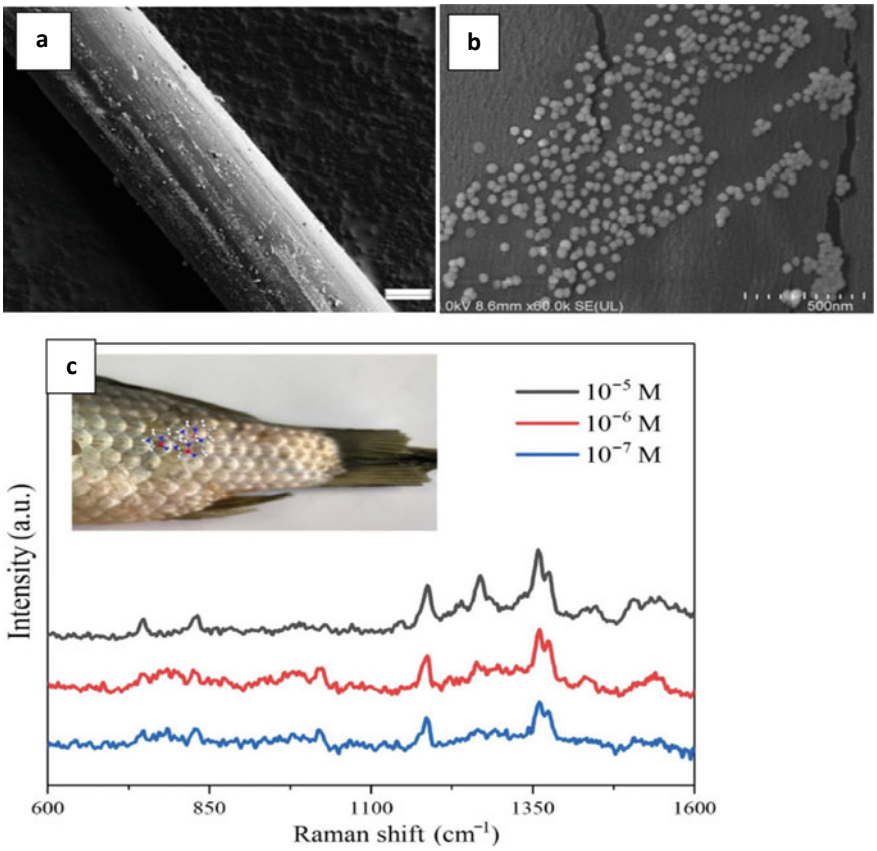

Fig. 4 SEM images of regenerated cellulose fiber **a** before and **b** after decorating Au NPs and **c** Swabbing detection of the DMZ from the surface of fish using fiber-Au as flexible SERS substrate [16]

from CA [44]. In this study, as shown in Fig. 5, HAp mixed CA solution was electrospun, and the electrospun nanofiber was treated with alcoholic NaOH solution for an alkaline deacetylation process that resulted in regenerated cellulose. Resulted of RC-HAp was further treated with $AgNO_3$ solution, followed by the reduction of Ag^{3+} as AgNPs using NaBH4. The deacetylation process resulted in RC with higher hydrophilicity than the CA. Herein, HAp stimulates osteointegration by improving the mineralization of fiber mat (by acting as nucleating agents in the Ca-P crystal formation on the fibers) during SBF treatment). Besides, AgNPs were used to inhibit the infection of 650 bacterial species and in in vitro studies, AgNPs incorporated RC composite completely inhibit *S. aureus* and *E. coli*. However, a high amount of AgNPs results in cytotoxicity against the chicken embryo proliferation of fibroblasts. This study proves that RC-NPs composites could act as highly biocompatible and biocomponents deliverable scaffolds for tissue engineering applications [44].

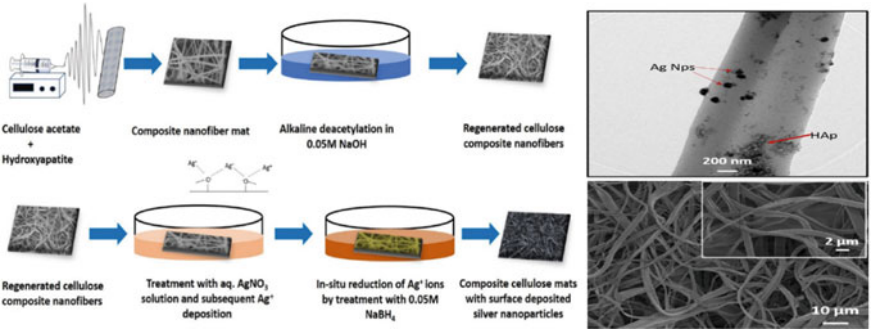

Fig. 5 A. Schematic representation of the fabrication of regenerated cellulose nanofiber mats containing HAp and Ag NPs. Sequential steps are shown to describe the various process involved in the fabrication process. B. Transmission electron microscopy (TEM) micrographs of regenerated cellulose nanofibers containing 1.5% HAp and treated with 7% $AgNO_3$, C. represents SEM image of pristine regenerated cellulose nanofibers. *Republished with permission from* [44]

4.5 RC—Graphene Composite for Biomedical Applications

RC—graphene/graphene oxide/reduce graphene oxide composite nanomaterial exhibits excellent properties such as high mechanical strength, thermal stability, hydrophilicity, and conductivity. Abundant oxygen groups (epoxide, hydroxyl, carbonyl, carboxyl) ease the moisture absence and modify with a wide range of biological molecules and polymers [45–47]. As shown in Fig. 6, abundant hydroxyl groups and carboxylic groups of graphene efficiently make a hydrogen bond with the hydroxyl groups of RC that consequent strongly forms a strongly grafted composite [48]. RC or other cellulosic materials are electrically insulative/inert materials. However, incorporating a significant amount of graphene nanomaterials into the RC cellulose efficiently enhances the conductivity property of the RC, which can be effectively utilized in bioelectronic and biosensor applications. In addition, enhanced hydrophilic properties of RC-GO composites confer great opportunity to make it a potential candidate for antimicrobial wound dressing and tissue engineering scaffold applications. For instance, Machnicka et al. (2018) produced an RC-GO membrane that efficiently inhibits bacteria and fungus growth [49]. In this study, RC-GO film was prepared by mixing cellulose solution (CEL) in 1-ethyl-3-methylimidazolium acetate (EMIMAc) and GO in N, N-dimethylformamide (DMF), followed by phase inversion membrane preparation method. The results of this study prove that a smaller size and significantly higher concentration of GO (2% w/w) added to the RC membrane strongly inhibit the Gram-negative (*E. coli*) and Gram-positive bacteria (*S. aureus*) as well as fungi of Candida albicans.

In another study, Chook et al. (2015) studied the antibacterial activity of Ag NPs decorated RC-GO membrane [50]. This study prepared the RC-GO membrane by mixing RC and GO in acetic acid, followed by the thin film casting. Next, the RC-GO membrane was immersed in the silver ammonia complex, $Ag(NH3)^{2+}$, in the

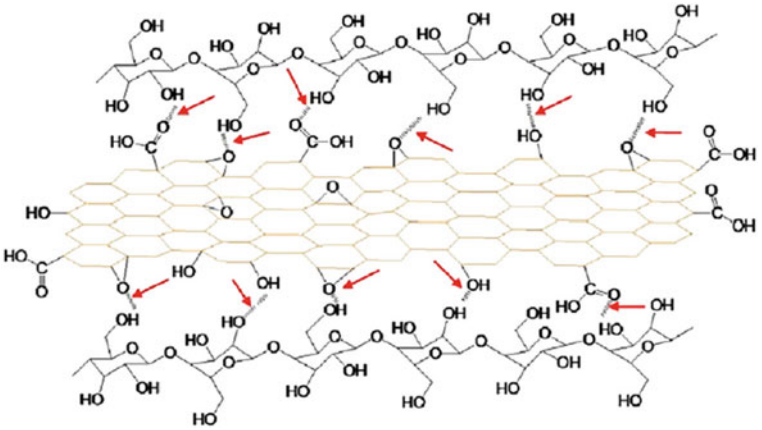

Fig. 6 Schematic representation of the interaction of GO surface and RC macromolecular chains, the redraws demonstrate hydrogen bonds. *Republished with permission from* [48]

presence of glucose that acts as a reducing agent of Ag^+ under microwave irradiation. Herein, negatively charged oxygenated functional groups of GO and hydroxyl group of -OH enhance the adsorption of Ag^+ ions. Notably, the RC membrane with 1 wt% GO yields 26 times higher amount of Ag NPs than the bare RC membrane. In addition, RC-GO containing membrane significantly reduces the Ag NPs released to the aqueous solution as GO facilitates the efficient encapsulation of Ag NPs into the membrane. Compared to the bare RC-Ag NPs membrane, the RC-GO-Ag NPs membrane showed higher inhibition against *S. aureus* and *E. coli* [50].

5 Surface-Modified Regenerative Cellulose for Biomedical Applications

5.1 Surface-Modified RC for Tissue Engineering

Tissue engineering is a complex discipline that has to steal the limelight as it has now become the new approach in regenerative medicine. This is due to its key strategies that facilitate and stimulate tissue repairment and restoration, which are crucial for the functional recovery of the specific organ. Conventional treatment like organ transplant can be limited since patients need to queue and wait for organ donation availability, which takes a long time as organ donation shortage has always been a critical issue. Even if they found one, other risks still need to be considered, such as failure in tissue matching, risk of infections, and lifelong immunosuppression [51]. Tissue engineering is an alternative method to organ transplant as it offers more benefits, including no major surgery required, and most importantly, it has a

lower likelihood of tissue rejection [52]. This field encompasses scaffolds that are combined with cells and incorporated with suitable growth or biochemical factors that help to promote tissue regeneration. It provides temporary structural support for tissue regeneration [53]. Therefore, research and development in this field are still going strong through discoveries of new materials and methods to produce more reliable scaffolds for a broader spectrum of applications. One of the methods that have been used is the surface modification of the materials.

The electrospun scaffold is implanted at the targeted area and left to integrate with the surrounding tissue. The materials used to fabricate the scaffold should possess good biocompatibility, biodegradability, and non-toxicity. Good biocompatibility and non-toxicity ensure no harmful side effects after the implantation, such as allergies, irritation, or inflammation [54]. The scaffold serves as a bioactive site to induce cell and tissue restoration. Therefore, the scaffold should have degraded when the new tissue is formed. The rate of degradation varied depending on the types of tissue. For instance, tissue for skeletal muscle requires a slow degradation rate since it needs to maintain the mechanical strength until the new tissue has been fully developed. As for skin tissue, it should not exceed more than a month and must have fully degraded by that time to avoid interference with the restoration of the tissue. The scaffold also should be bioresorbable so that when it has degraded, it can be naturally adsorbed by the body [55]. Cellulose met those prime requirements, making it a promising tissue engineering application candidate [56]. Nonetheless, cellulose scaffolds have overcome protein adsorption issues [57]. This issue is perturbing as one of the factors of failure of implants is a drawback from an inadequate amount of protein adsorption onto the scaffold's surface.

The extracellular matrix (ECM) comprises a fibrous network with various proteins responsible for tissue repair. The unfolding of the proteins determines the rate of protein adsorption. Thus, protein adsorption increases as protein unfolding increases since more functional protein groups are exposed to the implant's site. As protein adsorption increases, cell adhesion also increases where cell adhesion is the first interaction with the implant, followed by cell attachment, migration, differentiation, and proliferation for tissue regeneration [58]. Besides the rate of unfolding proteins, the size of the protein, charges of the proteins, and the surface also need to consider as they influence the protein adsorption. Hence, surface modification is necessary to alter the scaffold's surface topography and tune it into the functionalized scaffold to permit protein adsorption onto the surface of the scaffold [59].

RC exhibits favorable characteristics, making it a suitable material for tissue repair. The researchers studied the characterization of RC to determine whether it can satisfy the requirements needed to be used as alloplastic materials [60]. The morphological properties of RC are tunable depending on the desired tissue that needs to be repaired. RC's porosity can be adjusted according to its application. For instance, for soft tissue, the pore size needed ranges between 20–120 μm, whereas 100–300 μm is required for bone regeneration. As for crystallinity, RC has lower crystallinity when compared to native cellulose. This situation depicts a good turnout as a decrease in crystallinity increases water absorption and biodegradability. As the crystallinity decreases, the cellulose fibers become more disorganized and degraded easily. Next, RC has lower

thermal stability due to low crystallinity and low degree of polymerization. This thermal stability is also an essential feature for tissue engineering as it ensures the biodegradability of the scaffold. Other significant features that were tested include cytotoxicity, mutagenicity, and genotoxicity and based on the results obtained, RC did not show any potential for these to happen. Therefore, it can be confirmed that RC is non-toxic and suitable for tissue repair [60]. Despite having the mentioned beneficial properties, surface modification of the RC helps to boost the cell activities.

Filion et al. (2011) studied RC and chemically modified RC for application in bone tissue engineering. The modification method used is oxidation and sulfonation, producing sulfated cellulose fibrous meshes (SC). This method opts as sulfated polysaccharides possess higher affinity where it can preserve more endogenous proteins through the non-covalent electrostatic interactions between the sulfate residues and the basic amino acid residues of the proteins [61]. RC is oxidized using sodium periodate, where the aldehyde functional group has been successfully modified into 2-amino-ethyl sulfate groups. In terms of mechanical strength, both exhibit good ultimate tensile strength. SC can maintain megapascal elastic modulus and ultimate tensile strength when in water. As the scaffold is pressed to fit into the target area or needs to be stretched to cover the target area, good mechanical strength is a must to prevent the scaffold from rupturing easily. Besides, SC has a higher retention capacity of the recombinant human bone morphogenetic protein-2 (rhBMP-2) compared to RC, and more than 85% of the rhBMP-2 stayed biologically active even after 7 days.

Furthermore, cell attachment and osteogenic differentiation of the rat bone marrow stromal cells (MSCs) of SC are higher than the RC, with more than 100% increment 48 h after the cell seeding. Therefore, this research has proved that surface-modified RC improves cell attachment and differentiation activities while maintaining solid mechanical strength. Alizarin red staining is used to detect the deposition of the mineralized matrix after osteogenic differentiation of the MSCs. Based on Fig. 7, the alizarin red-stained more intensely for SC than RC, proving that cell attachment and differentiation activities are higher for surface-modified RC.

Pértile et al. (2012) demonstrated surface-modified RC for usage in nerve tissue engineering. The RC used in this research is bacterial cellulose (BC), and the technique used for the surface modification is by infusion of a peptide into the carbohydrate-binding molecule (CBM3). Peptides are the bio-sticker as they are adsorbed onto the scaffold's surface, allowing cell adhesion and stimulating cell proliferation. Two recombinant proteins with different peptides were fused to CBM3: IKVAV and (19)IKVAV. IKVAV is a bioactive molecule that can be naturally found in the ECM proteins and has been proved to promote the growth of Schwann cells for nerve regeneration [62]. The cells used in this research to test for the cell adhesion include SH-SY5Y human neuroblasts, N1E-115 rat neuroblasts, rat Pheochromocytoma (PC12), and rat Mesenchymal stem cells (MSCs). (19)IKVAV-CBM3 elevates cell adhesion for all types of cells tested, and the protein is enhanced by almost 100% for adhesion of PC12 cells. Furthermore, results of this study show that the cells adhesion of PC12 and MSCs is higher for (19)IKVAV-CBM3 compared to others. This study also focused on the secretion of the nerve growth factor (NGF). This is because,

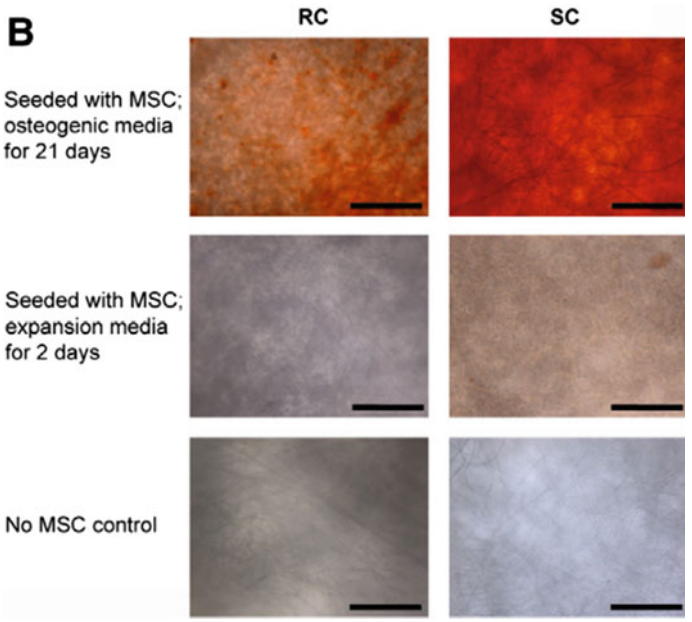

Fig. 7 Alizarin red staining of the MSCs cultured on RC and SC meshes in osteogenic differentiation media (top), expansion media (middle), and meshes without cells (bottom). *Republished with permission from* [61]

the scaffold produced for tissue engineering application should be able to mimic the functional microenvironment of the cellular. For instance, the natural environment of the cellular secretes growth factors that support the cell activities. Thus, the scaffold produced should also be able to induce secretion of the growth factor. In this research, (19)IKVAV-CBM3 secreted higher amount of NGF which is released by MSCs compared to the others. This result is attributed to the higher cell adhesion that occurred [29].

Another study carried out by Courtenay et al. (2018) substantiated that the cell attachment for surface-modified RC is higher than for unmodified RC. The RC was chemically modified through derivatization and crosslinking. During derivatization, the RC is modified via cationization with glycidyltrimethylammonium chloride (GTMAC), which produces cationic cellulose where the surface of the RC becomes positively charged. The cell used was the MG-63 cell line which is known as the osteoblast cell for bone regeneration. It also reported that the cell proliferated on the cationic surface besides cell attachment. Only minimal cell attachment can be observed for unmodified RC. Despite having surface-modified, the morphology of the modified RC is not affected, and it still has the same elastic modulus as the unmodified RC. This condition is because the phospholipid groups present in the cell membrane are negatively charged, which makes them attracted to the positively charged scaffold's surface, which causes the cells to attach to the surface of the

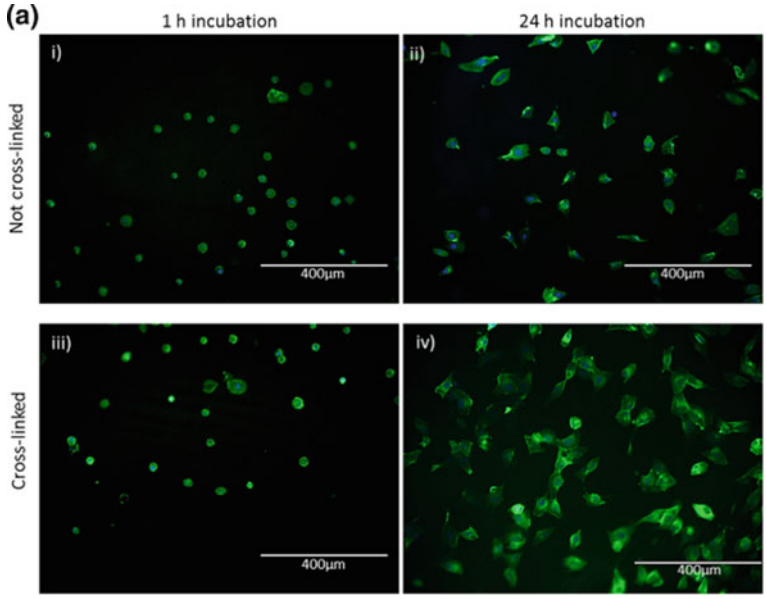

Fig. 8 MG-63 cells seeded on cationic cellulose for not crosslinked RC (i and ii) and crosslinked RC (iii and iv) [63]

scaffold. This study also demonstrated that the mechanical properties of the RC can be enhanced by surface modification. The RC is modified by a crosslinking technique where glyoxal was used as the chemical crosslinker. The bulk elastic and surface shear modulus of the cationic cellulose increases after it undergoes further surface modification via crosslinking. Moreover, based on Fig. 8, it can be proved that crosslinking enhances cell adhesion as the MG-63 cells appeared to spread out more vigorously in crosslinked RC compared to not crosslinked RC.

5.2 Surface-Modified RC for Drug Delivery Application

Drug delivery is also part of regenerative medicine and tissue engineering. The working principle of drug delivery is very straightforward as it works by loading and releasing the drug to the target tissue. It also ensures that the drug is released at an optimal rate so that there is no issue in multiple administration or overdose [64]. Drug-loaded scaffold plays a vital role in promoting tissue repairment and regeneration [65]. Scaffolds that are qualified for drug delivery must have homogenous drug dispersion throughout the scaffold, able to release drug according to the predetermined rate, low drug binding affinity, stable physical dimension, chemical structure, and biological activity longer duration of time. Low drug binding affinity allows ease of drug release as the higher the drug binding affinity, the more tightly the drug binds

onto the scaffold. Next, the scaffold should have maximum loading capacity release kinetics. Loading capacity release kinetics is the amount of drug that can be mixed into the scaffold. This condition ensures that the drug can be released continuously for a longer period. The amount of drug released have to be controlled so that the right amount of drug can be delivered to the cells from time to time [66].

Surface modification for drug delivery applications makes it easier for drugs to bind at the action site, especially for drugs that cannot be easily bound onto the surface, like hydrophobic and uncharged drugs. There are three essential factors for successful drug delivery: high colloidal stability in the bloodstream, low protein adsorption, and a suitable matrix used for drug entrapment. All of these can be achieved through surface modification. High colloidal stability in the bloodstream can be achieved by fixing water-soluble polymers or highly charged functional groups. Next, the protein adsorption is affected by the length of the attached polymer and the surface charge, which can be altered to obtain low protein adsorption. Unlike tissue engineering, in which higher protein adsorption indicates good results, drug delivery only needs low protein adsorption. As for a suitable matrix used for drug entrapment, cellulose has many functional groups; they are not suitable for drug binding. Therefore, surface modification by using suitable matrix ligands can produce a functional surface of the scaffold that binds drugs [67].

Badshah et al. (2018) reported that surface-modified RC is very effective in controlling drug release. The surface modification method used in this research is acetylation, where the BC was soaked in acetic acid. This method can maintain a large-modified surface area with controlled hydrophobic or hydrophilicity properties of the scaffold. It also offers compatibility with other composite materials and is non-tox. The drugs used were famotidine and tizanidine. Thermogravimetric analysis (TGA) shows that surface modification of the BC has improved its thermal stability. The pore size also decreased, and the microfibrils became thicker when analyzed using the scanning electron microscope (SEM). Scaffold loaded with famotidine has the highest drug loading percentage, attributed to the high drug dosage. As for drug release, surface modification with freeze-drying recorded more than 80% of drug release for tizanidine after 0.25 h. The percentage of drug release is higher than the drug loading. It may happen because the drug may be present on the surface of the scaffold instead of embedded properly into the scaffold, which explains why the drug can be released easily. It can be concluded that surface modification with freeze-drying is effective in controlling the drug release as it alters the hydrophilicity of the BC.

5.3 Surface-Modified RC for Wound Dressing Application

Skin is the largest organ of the human body that makes up the integumentary system, forming a barrier to protect against pathogens, regulating body temperature, and maintaining water-electrolyte balance. Damage to the skin causes bacterial infections that can harm the body system. Therefore, the wound dressing temporarily covers

and protects the wound area from bacterial infection. Wounds can happen because of burns, surgical incisions, trauma, or diabetes. Typical treatment for a wound dressing that is still applied in clinical includes the usage of mesh, gauze, plaster, and bandages. However, this treatment has a higher probability of getting the infection. It is also not biodegradable, which can cause secondary tissue damage when removing the mesh or gauze from the wound as it adheres to the wound [69]. Hence, many researchers have started to develop scaffolds for wound dressing application. Aside from facilitating, it also helps to accelerate tissue reformation during wound healing. Orlando et al. (2020) demonstrated that the surface of the RC can be chemically modified into an antibacterial wound dressing. This research is conducted because cellulose lacks in antibacterial features. The study demonstrates the usage of two different epoxides: glycidyl trimethylammonium chloride (GTMAC) and glycidyl hexadecyl ether (GHDE). First, the deprotonated surface of the hydroxyl group was obtained via ring-opening polymerization. The epoxides were added later through a base-catalyzed heterogeneous reaction under aqueous conditions. It was proven that for surface-modified BC, the bacterial population decreases by half compared to unmodified BC within 24 h of direct contact with *S. aureus* and *E. coli*.

5.4 Surface-Modified RC for Biosensing Application

Biosensors can be described as an analytical device that detects and measures biological interaction and convert it into a readable signal. It works through the recognition of biological reactions by the physicochemical detector. RC is hydrophilic, while some molecular sensors are hydrophobic, which requires surface modification of the RC so that it can be used to detect various active biomolecules like urea, lactate, glucose, genes, amino acids, cholesterol, and proteins [71]. It is now widely used as a diagnostic tool due to its favorable features that can give instant read-out so that the users can get real-time results [72]. A study done by Li et al. (2019) invented a biosensing device for glucose detection. The RC was modified by introducing an active carboxyl group via plasma-induced grafting polymerization and glucose oxidase (GOx), an enzyme for glucose detection that was chemically immobilized through EDC-NHS crosslinking reaction. Plasma-induced grafting polymerization to improve the stability of the bonded polymer. The content of physically encapsulated enzyme for chemically crosslinking modification is higher than RC, which was not modified through crosslinking. Besides, when the amount of encapsulated enzyme is higher, it increases the sensitivity of the biosensor as it can detect the lower concentration of glucose in a short time. The detection limit of the glucose concentration recorded was 0.003 M within 4 min.

6 Challenges and Future Prospective

The challenge in this field is to ensure that the properties of the scaffold are biocompatible and non-toxic due to the process during the surface modification since it uses additional chemical solutions that are toxic, which can cause future adverse effects. In addition, fabricating scaffolds that can mimic the ECM is the major challenge as the environment inside the ECM is particularly sensitive and only reacts if it can identify the scaffold has the features as the ECM, such as in nanometer scale and has a porous surface. Furthermore, the conditions of the ECM, such as the pH, temperature, and nutrients, also need to be taken into account as they can also affect cellular activities. Moreover, cell recognition is highly selective and only recognizes the ECM environment, which is crucial as it is the first stage before other cellular responses like cell attachment, differentiation, and proliferation occur. For instance, cell adhesion can only happen once cell recognition successfully distinguishes and verifies the ECM structure.

Next, the mechanisms for every process after implantation at the target area are also worrying since we cannot see what happens between the scaffold and the cellular microenvironment. While conducting the research, we can witness what happens during the cell study in vitro and in vivo. However, after implantation, we can only monitor the patient's condition from time to time. Even if the patient shows side effects, we cannot surely tell which part is the problem. Is it during cell adhesion or protein adsorption, or is the scaffold itself the problem? We cannot distinguish what went wrong. Thus, the mechanism is a paramount study as it justifies details of the implanted scaffold's failure and helps us improvise and produce a better scaffold.

Furthermore, the application of tissue engineering in some areas requires additional criteria. For example, for the regeneration of blood vessels and the esophagus, the scaffold should be able to withstand structure. This condition is essential because those blood vessels always contract and relax during blood pumping, and the esophagus also contracts and relaxes when swallowing food. Therefore, the scaffold should be very flexible and has high mechanical strength so that it has high resistance against the structure.

The applications are still in the preliminary phase and far from the clinical level. Thus, continuous research and development need to be done to fabricate a more reliable scaffold. Recent research has focused more on developing functionalized scaffolds through surface modification. Moreover, a study on drugs that accelerate tissue reformation with anti-inflammatory effects is also gaining attention in this research area. A combination of these efforts and the integration of stem cell therapy produce a scaffold that is qualified to be tested in clinical trials. A stem cell has been proven to stimulate the formation of new cells to replace dead cells. In the future, the scaffold can be used in a variety of applications.

7 Conclusion

RC is a naturally abundant, highly biocompatible, biodegradable polysaccharide widely used in biomedical applications such as wound dressing, scaffolding, and drug delivery. A high amount of readily available -OH groups allow a high drug loading rate, and a low degradable rate prolongs the duration of drug delivery. In tissue engineering scaffold applications, RC-based scaffold exhibited a high amount of cell adhesion and high cell viability rate due to its high number of functional groups, biomimicking molecular structure, less toxicity, high biocompatibility, and hydrophilic nature. Besides, high moisture absorption rate and high oxygen permeability make RC an ideal candidate for wound dressing applications. Similar to other cellulose materials, d-glucopyranose units linked to β-1,4-glycosidic bonds of RC cellulose cannot be readily metabolized by the human body. Although RC has excellent potential for tissue engineering scaffold or drug delivery applications due to the abundance of hydroxide functional groups, the low degradability of RC in the human body limits its usage. However, recent advancement in cellulose-based materials reveals that the degradability of cellulose inside the human body can be significantly enhanced by oxidizing cellulose molecules or opening d-glucopyranose rings. Therefore, oxidized RC could be the potential candidate for human body implantable scaffold or drug-delivering matrix. RC can be readily dissolved in derivatizing solvents or ionic liquids. This property allows RC to be synthesized in various topographical features such as nanobeads, nanobeads, and membranes with high porosity and surface area, which can be efficiently utilized in drug delivery, wound dressing and tissue engineering scaffold applications. However, the toxicity of this solvent remains a major challenge in biomedical applications. Therefore, further study is necessary to address a green non-toxic solvent that can be used to derive RC from the regeneration process and RC membrane synthesis process. Various nanomaterials, such as metallic nanoparticles and graphene nanomaterials, can effectively modify RC. AgNPs, CuOs, and ZnOs incorporated in RC composite materials exhibit high antibacterial activity. However, less solubility of RC remains a major challenge in controlled releasing the antibacterial NPs to the target area. In this context, proper nanoarchitectures such as RC-based nanofiber with high porosity or surface-modified RC– NPs composite may degrade easily and release the NPs effectively.

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Nanocellulose Materials and Composites for Emerging Applications

Titilope John Jayeoye, Fredrick Nwude Eze, and Sudarshan Singh

Abstract There has never been a time, where the use of environmentally friendly or green materials is in high demand than now. From the perspective of environment conservation and sustainability, conscientious applications of materials with none/minimal deleterious effects on the human ecosystem are being pushed to the front burner. In this wise, nanocellulose materials or simply cellulose in nanostructured form have become green materials of huge interest owing to their intrinsic physicochemical properties. High aspect ratio, mechanical ruggedness, biocompatibility, non-toxic, high availability, and their multitudinous hydroxyl groups which can be easily tuned through various chemical reactions present nanocellulose as an attractive substrate for modern applications. In this chapter, we will present nanocellulose materials and composites for emerging applications. We started the chapter with a brief classification of nanocellulose materials into nanofibers and nanostructured materials. The nanofibers comprise cellulose nanofibrils, cellulose nanocrystal, and bacterial cellulose, while the nanostructured materials are made up of cellulose microcrystals or microcrystalline cellulose and cellulose microfibrils. A brief explanation on the preparation methods, properties, challenges, etc., encountered toward full exploitation of these materials is further provided. We showcased a gamut of areas, with huge applications of nanocellulose materials in modern technology, including formulation of stable Pickering emulsions, composites with Metal nanoparticles (MNPs), and application in anti-cancer, anti-fungal and antibacterial agents, film packaging materials fabrication, water purification, in electrospinning for sustainable fabrication of processable nanofibrous membranes and, finally, in biomedicine (wound healing and medical implant application).

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Abbreviations

NaOH	Sodium hydroxide
HCl	Hydrochloric acid
$CaCl_2$	Calcium chloride
HBr	Hydrobromic acid
$NaBH_4$	Sodium borohydride
CNFs	Cellulose nanofibrils
CNC	Cellulose nanocrystals
MCC	Cellulose microcrystals or Microcrystalline cellulose
BNC	Bacterial cellulose
TEMPO	2,2,6,6-Tetramethylpiperidine-1-oxide
$NaClO_2$	Sodium chlorite
PVA	Poly (vinyl alcohol)
H_2SO_4	Hydrogen Tetra-oxo sulfate VI acid
AgNPs	Silver nanoparticles
AuNPs	Gold nanoparticles
CuNPs	Copper nanoparticles
FeNPs	Iron nanoparticles
PtNPs	Platinum nanoparticles
PdNPs	Palladium NPs
ZnO	Zinc oxide
Fe_2O_3 NPs	Iron oxide nanoparticles
TiO_2 NPs	Titanium oxide nanoparticles
PANI	Polyaniline
GO	Graphene oxide
4-NP	4-Nitrophenol
4-AP	4-Aminophenol
MO	Methyl orange
MB	Methylene blue
CR	Congo Red

1 Introduction to Cellulose Materials

Cellulose materials are special class of bio-based products that have gained significant prominence in the last decade, owing to their enormous availability, ease of generation, and unique physicochemical properties. In fact, cellulose is regarded as the

most abundant material/biopolymer found in the biosphere (part of the earth surface where life thrives), with about annual 50 billion tons production, since it can be found from diverse sources such as plants-comprising hardwood and softwoods, bacterial, algae, and tunicates [1]. **Plants materials** make up a huge cellulose source, owing to their abundance in nature, which is cheap, free, and very accessible. Plant-based sources of cellulose include corn, sugarcane bagasse, bamboo, rice, wheat, soybean straw, tomato peel, garlic residues, alfa, kenaf, mulberry fiber, sunflower, pineapple leaf, cotton fibers, etc. Wood sources, comprising hardwoods—eucalyptus, maple, oak, balsa, and elm and softwoods—cedar, pine, and spruce, etc., also make up a significant percentage of cellulose sourced from woods. With appropriate deployment of relevant technologies, plant-based cellulose source presents a sustainable avenue through which cellulose can be harvested for human usage. Another major source of cellulose in nature is from the animal-based source from algae, bacteria, and tunicates. **Algae-based** source presents abundance of cellulose, since the major cell wall components of many algae species are composed of cellulose [2], with the green algae accounting for the larger sources, while other groups (red and yellow algae) have also been found to produce cellulose). The crystallinity of cellulose sourced from algae is highly dependent on the species used, can be within 1–15% [3, 4], and can also vary with the seasonal variations and the maturity of the biomass materials applied [5]. Cellulose nanofibrils and cellulose nanocrystals are oftentimes the most easily processable class of cellulose form algae. For example, Wahlström et al. proposed a detailed extraction protocol of cellulose and cellulose nanofibrils (CNFs), from the green macroalgae *Ulva lactuca* [6]. The extraction process applied common alkali treatment (NaOH solution) and later acid treatment (HCl), to obtain the extracted cellulose component, while CNFs were obtained after dilution and homogenization, followed by freeze drying (Fig. 1).

In a similar scenario, Jackson et al. proposed a facile approach to obtain cellulose nanocrystal (CNCs) with carboxylic acid-rich functionality, from elephant grass (*Pennisetum purpureum*) leaves [7]. As shown in Fig. 2, the hydrothermal treatment of the milled grass, under NaOH and H_2SO_4 treatment, was for the removal of hemicellulose and other extracting components from the biomass (for acid treatment), while NaOH treatment would take out lignin components. The cellulose-rich components were further subjected to the popular TEMPO oxidation process, after which CNC was obtained.

Bacterial-based sources are very common sources of cellulose in nature. Certain bacterial species are indeed capable of using carbon and nitrogen sources in cultured media to generate cellulose microfibrils. Common species include Rhodobacter, Azotobacter, Rhizobium, Salmonella, Agrobacterium, Aerobacter, Pseudomonas, Sarcina, Acetobacter, Alcaligenes, Gluconacetobacter [8], etc. Bacterial-based cellulose presents the advantages of purity, unique nano-structural properties, and increased mechanical properties. Cellulose sources from tunicates are another very huge common sources of cellulose in nature. Tunicates are special class of marine invertebrates. Their huge enzyme complexes present at their epidermal layers or (tunic) are well known for cellulose production [9] and thus open another sustainable approach for humongous cellulose synthesis from biomass.

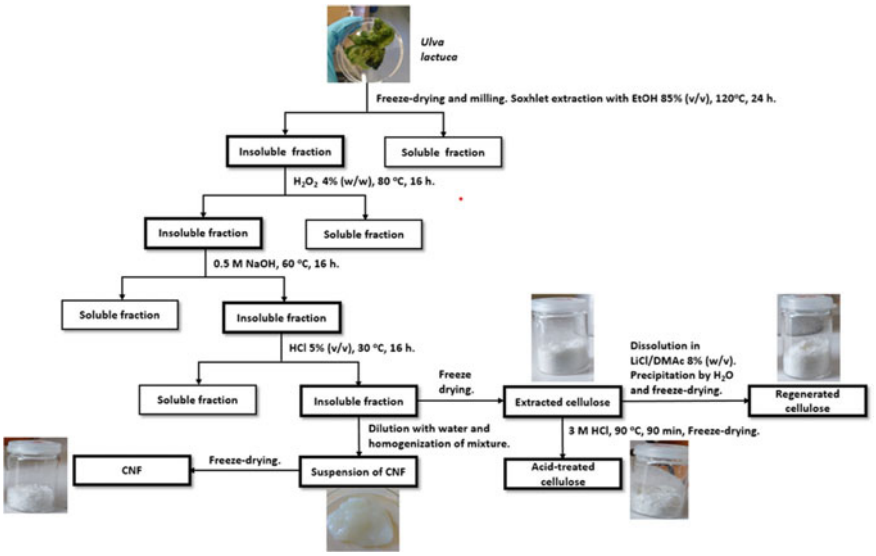

Fig. 1 Detailed extraction protocol of cellulose and cellulose nanofibrils from the green algae *Ulva lactuca*. *Republished with permission from* [6]. Copyright 2020, Springer

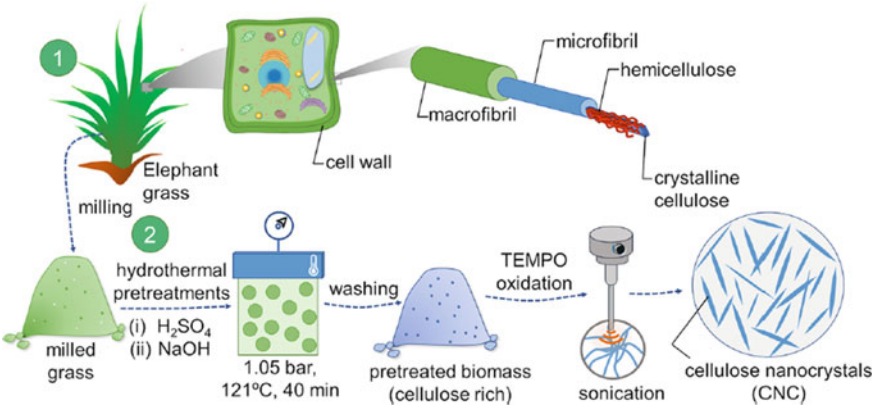

Fig. 2 Extraction details of cellulose nanocrystal (CNC) from Elephant grass, 1 shows the various cellulose compositions of plant cell wall and 2 shows the extraction protocol of CNC from the biomass. *Republished with permission from* [7]. Copyright 2021, American Chemical Society

Having expounded the major cellulose sources, we can now lay more emphasis on the basic categories of cellulose and center some discussions on the properties thereof.

2 Classification of Cellulose Materials

Cellulose by virtue of its structure is a natural polysaccharide consisting of several repeating units of β-D-glucose, unlike α-D-glucose units that mark starch polysaccharide. The β-D-glucose units of cellulose are linked together through intra-chain hydrogen bonding interactions, between the hydroxyl group of one unit and the oxygen of the next ring, to form β-1,4-glycosidic linkages [10], as shown in Fig. 3. This linear arrangement stabilizes the cellulose structure and thus confers additional structural rigidity on it. The degree of polymerization of the cellulose glucose units varies from one source to another.

Nanocellulose materials benefit from the perfect blend of cellulose and nanotechnology/nanoscience. As a result, they present an increased applications prospects of cellulose in biomaterials, optoelectronics, film fabrications [11], etc. Shortly, nanotechnology is an emerging scientific field which is concerned with the design, characterization, and applications of materials, at extremely low dimension of nanometer (nm) levels. The characteristic of materials at nano-level is quite distinct from the parent bulk materials, and thus, passionate interest is devoted to the modulation and tuning of materials at nanodimension. Figure 4 shows the different commonly available nanocellulose materials. Summarily, nanocellulose materials are divided into two major classes: nanofibers and nanostructured materials. The nanofibers are further divided into bacterial cellulose, cellulose nanocrystal or nanowhiskers, and cellulose nanofibrils. The nanostructured materials on the other hand are divided into cellulose microfibril or microcrystalline cellulose and the cellulose microfibrils [1, 11]. Nanocellulose also benefits from its high processability, biodegradability, biocompatibility, surface reactivity, purity, non-toxic, high crystallinity, high mechanical property, and light barrier property [12, 13]. These properties vary in the final cellulose materials depending on the parent cellulose source material, cellulose isolation strategy adopted, and the pre/post-treatment regimen used.

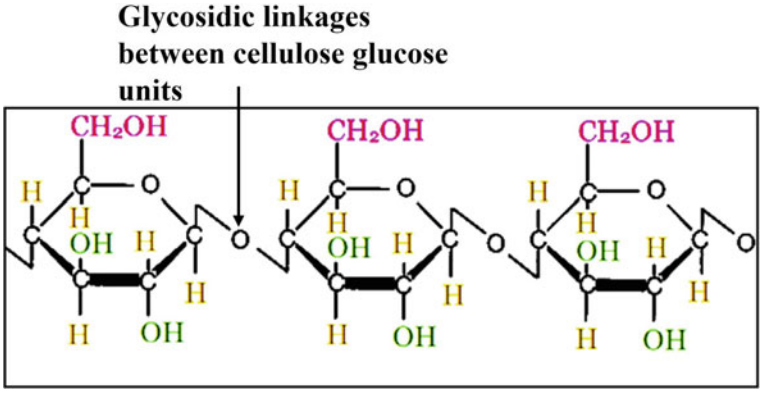

Fig. 3 Cellulose structure with modification. *Republished with permission from* [1]. Copyright 2018, Elsevier

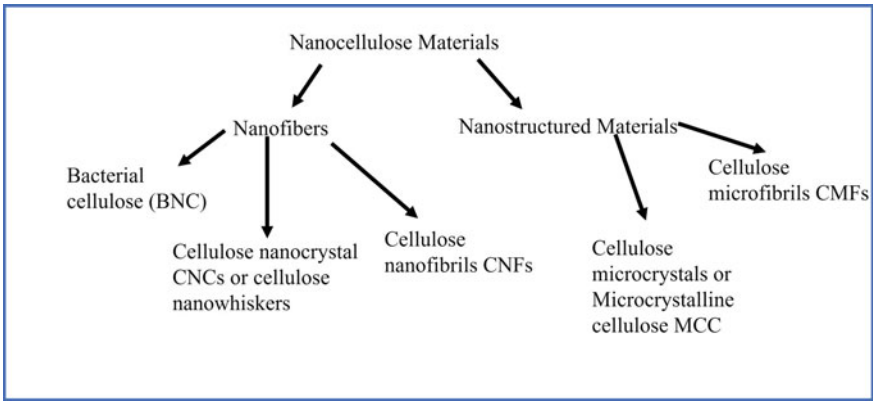

Fig. 4 Classification of nanocellulose materials, showing the commonly available cellulose-based products

2.1 Cellulose Microcrystal or Microcrystalline Cellulose (MCC)

Microcrystalline cellulose MCC is a purified and depolymerized cellulose obtained mostly from cotton and wood sources [14]. Through acid hydrolysis and alkali neutralization process, cellulose is broken down, with consequent reduction on the degree of polymerization. They have average sizes of about 10–50 μm in diameter. MCC generally shows high mechanical strength, high surface area, non-toxic, and biodegradability and thus forms a bioresource for the pharmaceutical industry [15]. MCC is the most commercially available source of cellulose from which other cellulose materials are produced [16, 17]. Major limitations with the use of MCC include its poor moisture absorption and poor wettability [18]. It is important to point also that the type of acid used for cellulose hydrolysis may play a role with regard to the thermal stability and crystallinity of the obtained MCC. Acid hydrolysis using HCl over H_2SO_4 has been reported to be better in this regard [19, 20].

2.2 Cellulose Microfibrils and Cellulose Nanofibrils (Nanofibrillated Cellulose)

Another form of nanocellulose is produced from mechanical vibration of cellulose using a high-pressure homogenizer, centrifuging, and other processing steps. Cellulose micro/nanofibers are mostly obtained from wood through mechanical disintegration leading to fibrils with dimension in the nano (<100 nm diameter) for cellulose nanofibrils and those much larger (>100 nm diameter) as cellulose microfibrils.

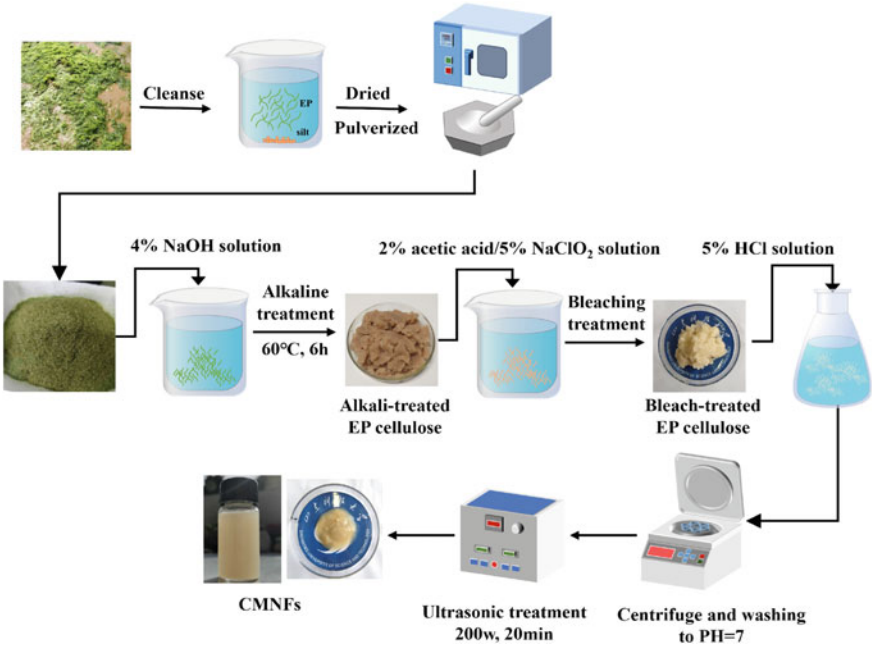

Fig. 5 Detailed steps for the preparation of cellulose microfibrils from Enteromorpha. *Republished with permission from* [21]. Copyright 2022, Elsevier

Zhang et al. gave a detailed synthesis step of cellulose microfibrils from Enteromorpha (a common green algae found in fresh-water stream) [21]. The first step of NaOH treatment is to break down covalent interactions between the lignocellulosic compartments to release cellulose [22], which was treated to $NaClO_2$ bleaching steps. Further HCl and ultrasonic treatment was employed to obtain cellulose microfibril (Fig. 5).

Similarly, Tian et al. obtained cellulose nanofibril from bleached Eucalyptus wood pulp, through acid hydrolysis, where the final step involved passing the suspension through a high-pressure homogenizer to obtain cellulose nanofibril [23].

2.3 Cellulose Nanocrystal (CNC) or Cellulose Nanowhiskers

Cellulose nanocrystal, with other common names such as cellulose whiskers, cellulose nanowhisker, or nanocrystalline cellulose, is rod-shaped or whisker-shaped image, often obtained from wood fiber, plant fiber, etc., through acid hydrolysis, as explained prior (Fig. 1 and 2). Common acids used include HBr, HCl, H_2SO_4, oxalic acid, etc., among which, H_2SO_4 and HCl have emerged the standard acid

hydrolysis reagents. They are highly crystalline (57–88%), aspect ratio of about (3–5 nm diameter and 50–500 nm length). Aside from CNC obtention from biomasses (Figs. 1 and 2), CNC is also often obtained from the hydrolysis of commercially available MCC. For example, Hanif et al. exploited AgNPs deposited on CNC for bacterial contaminated water purification [24]. The MCC used was from commercial (MCC; Avicel® pH-10.1, ~ 50 μm), which was subjected to acid hydrolysis using H_2SO_4. Polyaniline/CNC composite has also been reported, using H_2SO_4 hydrolysis from commercial MCC from Zhejiang Haizheng Biomaterials Co., Ltd., China [25]. While H_2SO_4 and HCl have been the most adopted hydrolyzing agents, H_2SO_4 can react with the multitudinous hydroxyl group of cellulose in solution during preparation and thus yield negatively charged CNC with surface sulfate esters group. The repulsion from similar negatively charged groups further increases the water dispersibility of the formed CNC. HCl hydrolysis on the other hand does not impart special charges on the formed CNC. The SEM images of CNC are shown below in Fig. 6.

Moreover, the special properties of cellulose types, cellulose nanocrystal, cellulose nanofiber, and cellulose microfiber are summarized in Table 1.

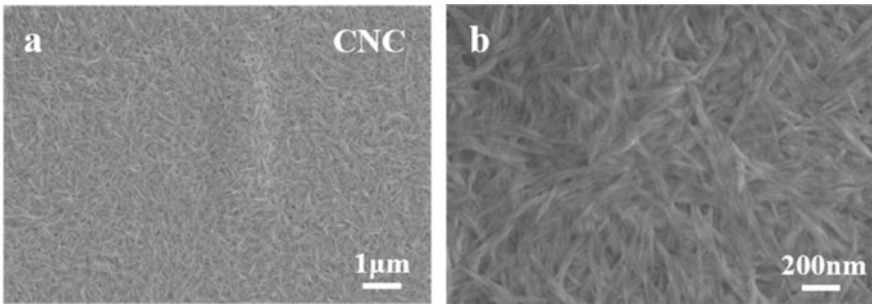

Fig. 6 SEM images of CNC at **a** 1000 and **b** 200 nm magnifications. *Republished with permission from* [25]. Copyright 2021, Elsevier

Table 1 Properties of common cellulose types, adapted from [26]

Cellulose type	Surface area (m^2/g)	Crystallinity	Young modulus (GPa)	Diameter	Length
Cellulose nanocrystal (CNC)	200	90%	50–140	5–30 nm	100 nm
Cellulose nanofibers (CNF)	100	50–90%	50–160	10–80 nm	<10 mm
Cellulose microfibers (CMF)	$<1.0 \times 10^6$	<60%	20	10 mm	>10 mm

2.4 Bacterial Cellulose (BC)

Bacterial cellulose, also known as microbial cellulose, is synthesized from certain class of bacteria, from microbial fermentation steps. BC can be secreted extracellularly by certain groups of bacteria, such as Salmonella, Agrobacterium, Pseudomonas, and Rhizobium. Low molecular weight carbon sources (D-glucose) are utilized as energy sources, through some biotechnical processes [12]. The bacteria are grown in appropriate nutrient media, after which BC is excreted as exopolysaccharides, as thick gel with 3D porous network of nanofibers. The microstructural property of BC produced is dependent on the source/kind of starting materials used. The polymerization degree of cellulose in BC ranges from 2000 to 6000, in comparison with 12,000 and 13,000 present in natural cellulose. Moreover, BC is about 10–50 nm in diameter and about 100–1000 nm in length [27]. BC can also serve as a substrate for the preparation of other cellulose nanomaterials such as NFC and CNC [12, 28]. The culture media conditions play critical role in determining the property of BC synthesized. This can be affected by factors such as pH of the media, temperature, media carbon, and nitrogen sources of carbon-(glucose, fructose, starch, xylose, maltose), while nitrogen source includes peptone and casein hydrolysate. Other parameters affecting BC culture media are oxygen concentration, agitation, or static synthesis condition [29].

3 Nanocellulose Materials Composites and Applications

Here, we aim to expound various applications of nanocellulose materials in composite with other notable materials. Nanocellulose materials function as supports with a view to imparting synergistic advantages, through modulation of the microstructural properties of the new composites.

3.1 Nanocellulose Materials in Pickering Emulsifier Formation

Nano-emulsion is emulsion with dimension in the nano-range (<100 nm). Emulsifiers (surface-active materials for droplet breaking) allow for easy dispersion of two naturally immiscible components, e.g., water and oil. The addition of oil to water for instance would form a two-phase immiscible solution. The addition of an emulsifier would break down the repulsive forces keeping the liquids away and forming a single-phase dispersion containing droplets with sizes (100 nm) and diameters between 20 and 200 nm. Thus, nano-emulsions are immiscible liquids (oil and water), which by the addition of an emulsifier can form a single-phase dispersion [30]. The balanced intermolecular interplay between the emulsion and the emulsifier prevents particle

aggregation and thus opens nano-emulsion materials for diverse applications in the food, cosmeceutical, pharmaceuticals, etc. Moreover, the special interaction between emulsifiers and the emulsion confers better advantages over the other emulsion types (micro- and macro-emulsions). Two major common classes include oil-in-water (O/W) and water-in-oil (W/O). Solid particles with capacity to penetrate and accumulate at O/W interphase are called Pickering emulsion. They provide enormous stabilization, resistance to coalescence, tunability, and improved elastic responses [31]. Biomolecules-based Pickering emulsion comprising diverse promising bio-based materials have been extensively reviewed recently [32]. Nanocellulose materials make a significant member of bio-based materials and will further be discussed herein.

However, it is important to mention some of the fabrication methodologies applied in Pickering emulsion formation. These include micro-fluidization, high-pressure valve homogenization, sonication, ultrasonication and ultra-filtration, and spray drying. Table 2 shows some reported Pickering emulsions based on cellulose nanomaterials, with further emphasis on their applications. Overall, the good viscosity and aqueous hydrophilic properties of nanocellulose materials are beneficent to their roles in providing stability in Pickering emulsion formulation.

3.2 Nanocellulose Materials Composite with Metal Nanoparticles (MNPs) and Their Applications

Metal nanoparticles (MNPs) by virtue of their unique physicochemical properties include high surface area-to-volume ratio, small size, facile surface tunability, and catalytic and surface plasmon resonance property (SPR). Surface plasmon resonance is defined as the resonant oscillation of surface conduction electron on metal surfaces, arising from photons in incident electromagnetic light [41]. However, SPR attributed to MNPs surfaces in solution is termed localized surface plasmon resonance (LSPR). At the LSPR of MNPs, colloidal solution exhibit highest stability and maximum absorption. Thus, this phenomenon imbues MNPs with wide applications in energy, catalysis, sensing, and drug delivery. Two major synthesis strategies involved include top-down and bottom-up approaches. The top-down synthesis approach is achieved by breaking the bulk materials into smaller fractions of monomeric nano-sized particles through physical and chemical processes, such as etching, lithography, cutting, and grinding. Bottom-up method involves the assembly from metal ions using reducing agents to generate small atomic nuclei which can grow and mature into mono- or poly-dispersed colloidal nanoparticles [42]. The two approaches present their uniqueness in diverse ways; however, the bottom-up approach, which involves the use of environmentally benign materials, has attracted enormous scientific interests over the past few decades. This may be so, as the use of materials with no or less environmental toxicity is preached on account of ecosystem sustainability. MNPs gold, silver, copper, zinc, platinum, and palladium are of huge biomedical,

Table 2 Nanocellulose-based Pickering emulsion formulation and their applications

Nanocellulose materials	Particles size (nm) and shape	Aqueous and oil phase	Droplets size (μm) and type	Comments	References
Bacterial cellulose/BSDF		Water; soybean oil	<30, O/W	Good stabilization against O/W emulsion over 1 month was obtained. The introduction of BC and BSDF was tested as a replacement for fat in biscuits	Xie et al. [33]
Methylated MCC	11–16, porous and open-cell structure	Water, dodecane, and soybean oil	O/W	Methylated MCC enhanced the stability of O/W Pickering emulsion, owing to their high viscosity and gel-like property	Ahsan et al. [34]

(continued)

Table 2 (continued)

Nanocellulose materials	Particles size (nm) and shape	Aqueous and oil phase	Droplets size (μm) and type	Comments	References
Wood-based oxidized CNC	Spherical, prepared by ultrasonication	Water, hexadecane	2.4, O/W	Strong electrostatic repulsion between O-CNC and its smaller sizes resulted in improved stability of emulsion, against centrifugation and thermal treatment	Gong et al. [35]
Bacterial cellulose nanofiber	10–30, spherical, prepared through High pressure homogenization,	Water, peanut oil	15 nm, O/W	0.05% BC nanofiber at neutral pH was enough for emulsion stabilization, by reducing the surface tension at interphase	Zhai et al. [36]
Soy protein isolate (SPI)/bacterial CNFs	Hollow smooth spherical structure, prepared by High pressure microfluidization	SPI, BCNF in water/ soybean oil	<1, O/W	The BCNF content plays a significant role on the emulsion stability. BCNF inhibited lipid hydrolysis, which influenced its capacity to be spray-dried into powder	Zhang et al. [37]
CNFs	Ultrasonication probe homogenization	Cellulose nanofiber solution/peanut oil	2.5–7.0, O/W	CNF stabilization improved room temperature stability for over 3 months, even in the presence of 0.1 M NaCl solution. This is attributed to steric hindrance effect mediated by CNF concentrations	Liu et al. [38]

(continued)

Table 2 (continued)

Nanocellulose materials	Particles size (nm) and shape	Aqueous and oil phase	Droplets size (μm) and type	Comments	References
Cellulose nanocrystal (CNCs)	Spherical, prepared by homogenization	CNC solution/ mineral oil	5–30, O/W	Owing to the presence of huge surface OH groups in CNC nanoparticles, strong interactions are feasible through hydrogen bonding and thus provide high surface stability to the formulated Pickering emulsion	Miao et al. [39]
Spherical-CNCs	Homogenization	S-CNC solution in NaCl/hexadecane	2.5, O/W	S-CNCs enhance emulsion stability over 7-days attributed to the low droplet size arising from the use of S-CNC particles	Dong et al. [40]

BSDF = Bamboo shoot water-insoluble dietary fiber; MCC = Microcrystalline cellulose; CNFs = Cellulose nanofibrils; NaCl = Sodium chloride

food, and pharmaceutical applications. Stable and highly dispersed AuNPs are of ruby red color, with characteristic maximum absorption at between 520 and 530 nm, depending on the synthesis condition adopted [43–46]. AgNPs on the other hand show sparkling yellow color to dark brown color with maximum absorption between 393 and 430 nm [47–50]. Copper nanoparticles on the other hand show absorption maximum at 472 nm [51].

Among the available MNPs, AgNPs are indeed about the most explored for food safety, owing to its high antibacterial activity, against diverse bacterial strains. Noronha et al. reported the fabrication of antibacterial AgNPs using CNCs generated from elephant grass plant, through initial pre-treatment to realize cellulose fibrils [52]. The obtained cellulose fibril was further subjected to TEMPO oxidation process to generate CNCs, which was applied as matrix/stabilizing agent for $NaBH_4$-mediated synthesis of small-sized AgNPs (CNC-AgNPs). The synthesized CNC-AgNPs were applied as anti-biofilm formation agent, against common bacterial strains—*E coli and B subtilis*, by coating on a Poly (vinylidene fluoride. PVDF) filter surface.

It was found that the CNC-AgNPs-treated surface exhibited improved anti-biofilm formation, through synergistic effect from CNC on one hand and the release of embedded Ag^+, in the CNC matrix, which can further facilitate DNA integrity compromise and other organelles. The mechanistic basis as detailed in Fig. 7 is tagged "attacking-attacking" in which CNC pierced through bacterial cell membrane and induced cell killing and Ag^+ released from CNC-AgNPs and induces its cell membrane damage through binding with sulfur and nitrogen groups present in proteins and enzymes and by harming DNA through reactive oxygen species (ROS) generation.

Another method of MNPs impregnation in nanocellulose materials is the depositional approach; through which, films or cellulosic fabrics are immerged in aqueous solution of MNPs under vigorous stirring treatments. In this wise, Sharma et al. deposited small-sized CuNPs in cellulosic fabric through $NaBH_4$-mediated reduction of copper sulfate salt in a beaker [53]. The CuNP-treated fabric showed enhanced antibacterial activity against gram negative bacterial—*E coli*—and gram positive—*S aureus*, strains.

Moreover, Ayyappan et al. investigated the effect of AuNPs, AgNPs, and graphene oxide (GO) in leather-like BC material, to assess the impact of the impregnated nanomaterials [54]. It was observed that AgNPs could impart high antibacterial activity, AuNPs could bridge the porous structure of BC membrane and impart hydrophobic properties, as revealed from the contact angle result, while GO would impact on the mechanical property of the composite. Cellulose nanomaterials-based anti-fungal property was investigated by Lloren et al. [55]. In their work, cellulose fiber was impregnated with copper sulfate solution, which was then subjected to two reduction methods, viz. physical (heat treatment and UV treatment) and chemical reduction process, using $NaBH_4$. The fabricated cellulose copper-based composite demonstrated high anti-fungal activity against *S. cerevisiae,* as putative fungus.

AuNPs in situ reduction using $NaBH_4$ in CNC matrix was reported by Wang et al. [56]. NaBH4 would facilitate the effective reduction of gold salt added in CNC matrix to furnish AuNPs of small size which was adduced to be beneficial to its

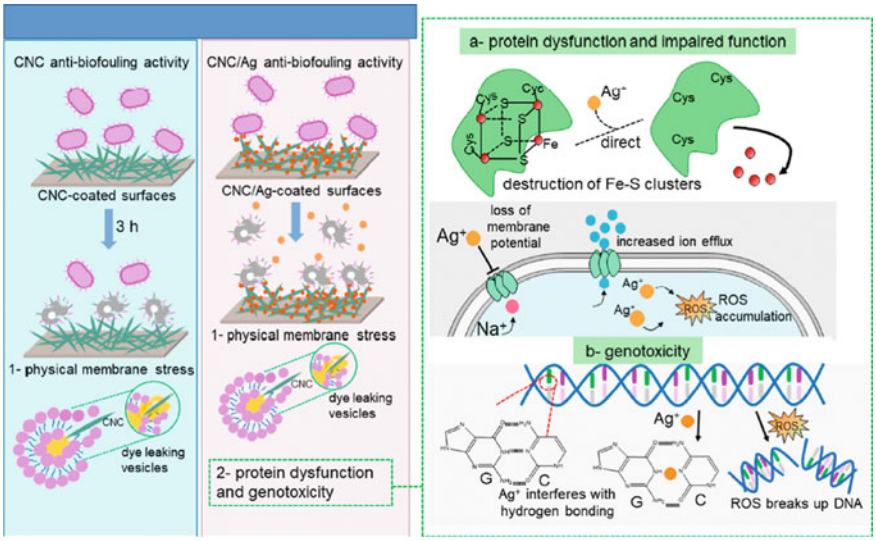

Fig. 7 Depiction of attacking-attacking mechanism of CNC-AgNPs on PVDF filter surfaces as anti-biofilm formation agent, in which both CNC and Ag^+ released from CNC-AgNPs offered synergistic effect on bacterial cell membrane. *Republished with permission from* [52]. Copyright 2022, American Chemical Society

catalytic reduction of p-nitrophenol as a model pollutant. It can be observed that MNP composite with nanocellulose materials provides an environmentally friendly approach for maximizing the applications of nanocellulose materials.

3.3 Nanocellulose Materials/Composites in Water Purification: Catalysis, Photocatalysis, Adsorption of Contaminants (Heavy Metals)

Water is the most important natural resource needed for the sustenance of economic and physiological activities, by man [57]. Arising from human industrialization and energy need is the concomitant pollution of available water for human consumption. Thus, scientific efforts are devoted to using different treatment strategies to process contaminated water for use. Nanocellulose materials have attracted huge interest owing to their strong mechanical strength, high surface area-to-volume ratio, biodegradability, and biocompatibility. The catalytic and adsorption property of nanocellulose materials may be greatly improved through composite with inorganic nanomaterials such as graphene and graphene oxides, AuNPs, AgNPs, PtNPs, PdNPs, FeNPs, Fe_2O_3 NPs, and TiO_2 NPs. The catalytic property of nanocellulose materials might be well related to their aqueous stability, which will provide good surface stability and supports for the embedded nanomaterials and, thus, protect

the composite from facile degradation or aggregation especially in highly complex samples.

3.3.1 Nanocellulose Materials/Composites in Catalysis

With the upsurge in the use of dyes and other coloring materials in the textile industries, the need for waste treatments, to safeguard the ecosystem from the deleterious impact of such wastes, cannot be over-emphasized. Dyes generally are complex organic compounds with capacity to induce materials coloration. Dyes give water bad coloration, thus diminishing water aesthetics and its usability. Other major industries relying on the use of dyes in large quantities include paper, food, leather, pulp, plastics, and pharmaceuticals. Dyes can be classified into basic, acidic, neutral, azo, anthraquinone, and reactive dyes, of which, azo dyes, containing the azo linkages (-N = N-), make up the most applied groups of dyes in the textile industry [58]. Figure 8 shows the structures of some commonly used azo dyes in the textile industry.

Nitrophenols are other class of hazardous wastes that is generated from multiple industrial organizations. 4-nitrphenol is one of the most common nitrophenols, with huge toxicity index, and it is listed on the priority hazardous list. The use of nanocellulose materials in the fabrication of catalytic devices for water/wastewater dyes degradation is premised on the capacity of such catalyst to provide faster reaction pathway that enhances the interaction between dyes molecules and the electron-supplying

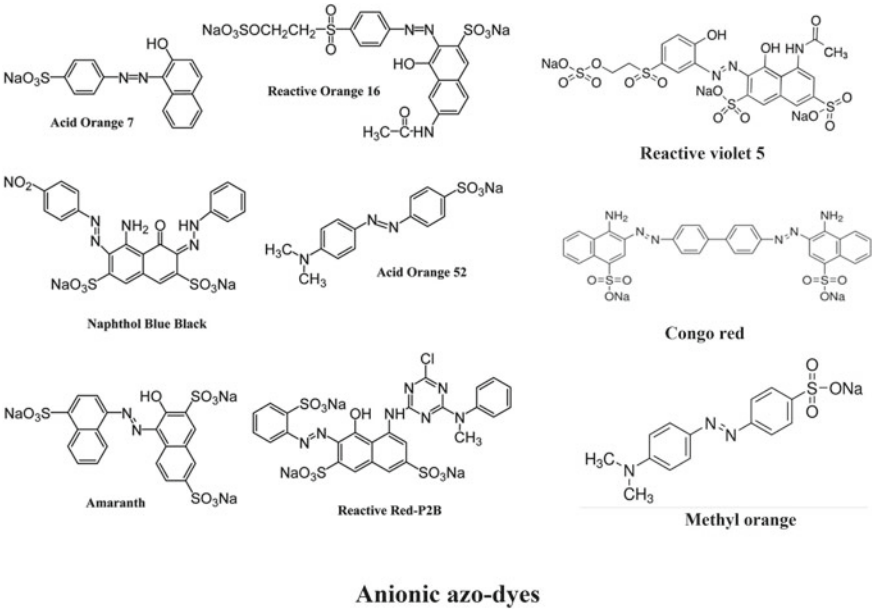

Fig. 8 Structures of some common azo dyes used in the textile industry

species. Nanocellulose materials composites with metal and metal oxide nanoparticles hold exciting prospect, through synergistic interaction between cellulose materials and the metal nanomaterials.

Deshmukh et al. reported the immobilization of Ag and AuNPs in bacterial cellulose nanofiber (CNF), film *using punica granatum* peel extract (PPE), as biological reducing to fabricate a completely eco-friendly support for the catalytic conversion of 4-NP to 4-AP [59]. The as-synthesized film was soaked in PPE extract, so that the extract would percolate and access the internal structure of the film. The film was rinsed in distilled water and oven-dried. The CNF/PPE composite film was further immersed in Ag and Au salts, after which color changes were observed, as a result of in situ reduction of metal salts in the CNF film matrix. The film was tested as a nanocatalyst, toward the conversion of 4-NP to 4-AP, with good rate constant value. The high catalytic property of the CNF film was attributed to the multitudinous phenolic components of PPE extract immobilized in the matrix, which can form π-π stacking interaction with the contaminant (4-NP), and thus hold it in near proximity, on the catalyst surface. The small size of the nanoparticles Ag and Au (15–20) nm, which are widely distributed in the CNC matrix was also adduced for the efficaciousness of the material. In similar light, Wu et al. synthesized, highly stable and dispersed AuNPs in CNC matrix through hydrothermal condition at 121 °C, for the conversion of 4-NP to 4-AP [60]. Unlike the previous work [59], here CNC was used as the reductant and the stabilizing agent for the composite formation. It was stated that at high temperature supplied from the hydrothermal set-up, the active reductive functional groups in CNC can be activated and thus mediate the reduction of gold salt. The catalytic efficiency of the synthesized composite was attributed to the small size of the AuNPs formed (10–30) nm.

Moreover, nanocellulose-based catalytic conversion/degradation of azo dye has been investigated and reported by Kamal et al. using zero-valent copper nanoparticles in cellulose nanofiber matrix [61]. Cellulose nanofiber in form of filter paper (FP) was soaked in aqueous solution containing chitosan and copper salt. It was then rinsed with distilled water and later soaked in $NaBH_4$ solution for the reduction of Cu^{2+} to Cu^0. $NaBH_4$, being a strong chemical reductant, will facilitate facile impregnation of CuNPs in the FP matrix. This was then tested as a nanocatalyst toward the reduction of methyl orange (MO) dye. The catalytic property of metal nanoparticles doped substrates (nanocellulose materials inclusive) is based on electron transfer/relay process, between electron-rich $NaBH_4$ (nucleophile) and electron-deficient contaminant (dyes) or the electrophile. The two species are brought in proximity on the nanocatalyst surface, by absorption thus acting as a relay system for successful electron transfer between dyes and $NaBH_4$ [47, 56, 62, 63]. As depicted in Fig. 9, $NaBH_4$ in the presence of water is hydrolyzed to $B(OH)_4^-$ and reactive hydrogen, which is adsorbed on the catalyst surface. The active hydrogen then reacts with 4-NP to generate 4-AP, a non-toxic reaction by-product. Since the concentration of NaBH4 is always much higher than the dyes, the reaction is often fitted into a pseudo first-order reaction, with equation, $\ln A_t/A_0 = -K_{rtn} \times t$, where A_t and A_0 represent the absorbance at the maximum wavelength of dyes at time t and the reaction start, and krtn is the rate constant (s^{-1} or min^{-1}).

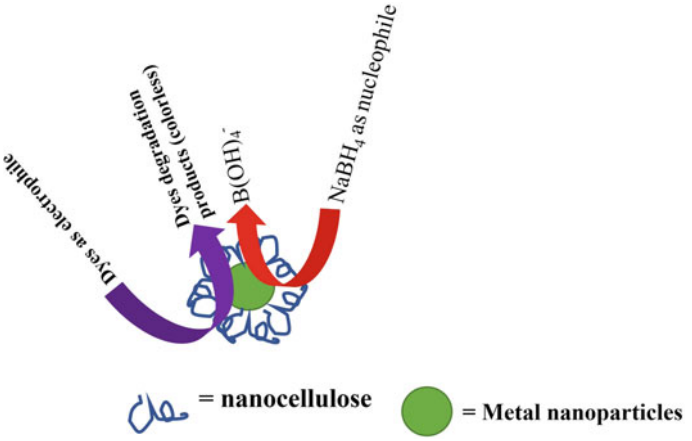

Fig. 9 Depiction of general contaminants reduction in the presence of strong $NaBH_4$, mediated by nanocellulose materials derived metal or metal oxide nanoparticles

Other reported nanocellulose-based contaminant catalytic reduction is summarized in Table 3.

Aside from the commonly investigated catalytic conversion of dyes and contaminants, nanocellulose-based MNPs doped composites are also used in catalyzing the coupling of some notable reactions in aqueous solution. For instance, the coupling of an alkyne, amine, and aldehyde, often termed the A^3 coupling, requires the presence of stable heterogenous catalyst. Thus, Wang et al. synthesized AuNPs in CNC/graphene matrix through hydrothermal synthesis condition at 120 ^{0}C for 10 h [70]. The fabricated AuNPs/CNC/graphene composite was successfully applied to the A^3 coupling reaction in aqueous solution, exhibiting yield, over 90% for ten recycling. Moreover, PdNPs-based cellulose catalyst for Suzuki reaction (between phenylboronic acids and arylbromides) and Heck reaction (aryl halides and olefins) have been reported with excellent catalytic efficiency attributed to the cellulose matrix providing high stability for the deposited PdNPs [71].

3.3.2 Nanocellulose Materials/Composites in Photocatalysis

Unlike the catalytic reduction of contaminants discussed prior, where strong reducing agent like $NaBH_4$ is required for providing electron for reaction success, photocatalytic reaction requires the activation from a UV (ultraviolet) light, sunlight, or other common light sources. The light source should have high energy and greater the band gap energy of the material. This technique holds great promise in water and wastewater treatment and decontamination regimen. It is also applied for air purification, hydrogen generation, etc. The band gap between particles is a critical determinant for the photocatalytic set-up. Each particle has its distinct band gap, which must be

Table 3 Reported nanocellulose-based metal nanoparticles doped composites for catalytic degradation of contaminants/pollutants

Nanocatalysts	Contaminants/pollutants	Kinetic rate constant (s^{-1} or min^{-1})	Comments	References
CNC@Au	4-NP to 4-AP	0.141 min^{-1}	AuNPs in CNC matrix using $NaBH_4$ as reductant. Small-sized AuNPs were realized in CNC matrix which enhances the conversion of 4-NP to 4-AP., with high stability over three runs	Wang et al. [56]
TEMPO-oxidized cellulose/PtNPs (TOCN/PtNPs)	4-NP to 4-AP	0.319 min^{-1}	Ethylene glycol or water-mediated synthesis of PtNPs in TOCN aqueous solution and heating at 110 ^{0}C	Pawcenis et al. [64]
Ag/NCC	4-NP and MO	K = 8.3×10^{-3} s^{-1} for 4-NP and 12.3×10^{-3} s^{-1} for MO	NCC mediated reduction of Ag salt at 65 ^{0}C for 2 h	Heidari and Karbalaee [65]
Ag/CTAB/ NCC	4-NP and MO	K = 5.4×10^{-3} s^{-1} for 4-NP and 14.2×10^{-3} s^{-1} for MO	$NaBH_4$-mediated reduction of Ag salt in CTAB modified nanocrystalline cellulose matrix	Heidari and Karbalaee [66]

(continued)

Table 3 (continued)

Nanocatalysts	Contaminants/pollutants	Kinetic rate constant (s^{-1} or min^{-1})	Comments	References
Pd/mPDA/BNC	4-NP, MO, MB	$K = 6.2 \times 10^{-3}$ s^{-1} for 4-NP, 8.8×10^{-3} s^{-1} for MO and 3.9×10^{-3} s^{-1} for MB	$NaBH_4$-based reduction of Pd salt in mPDA aqueous solution, to synthesize stable and small-sized PdNPs, into which BNC hydrogel was immersed for nanomaterials percolation and immobilization	GholamiDerami et al. [67]
CNF/PEI/AgNPs aerogel	4-NP, MB, CR	$K = 3.6 \times 10^{-3}$ s^{-1} for 4-NP, catalytic efficiency (99.2 for MB & 96.4 for CR)	CNF was modified with PEI through electrostatic interaction for Ag^+ anchoring, which was then reduced by dipping in $NaBH_4$ solution	Zhang et al. [68]
CNC/PEG/AuNPs	4-NP	$K = 1.47 \times 10^{-2}$ s^{-1}	CNC and PEG mixture was heated with gold salt at 80 ^{0}C, to achieve AuNPs of sizes <10 nm	Yan et al. [69]

CTAB = Cetyltrimethylammonium Bromide; mPDA = Mesoporous polydopamine; PEI = Polyethylene imine; PEG = Polyethylene glycol

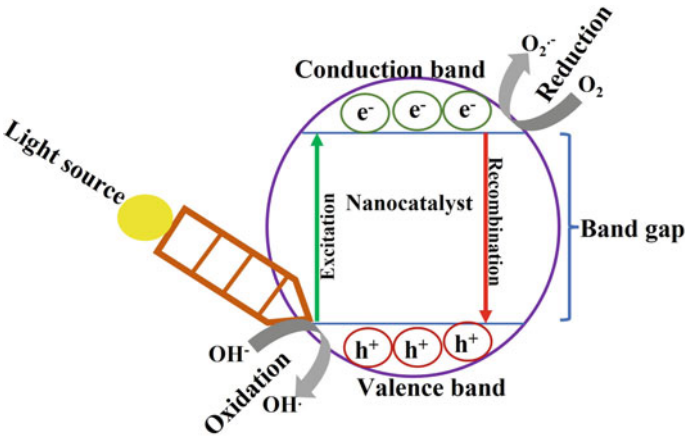

Fig. 10 Pictorial depiction of the mechanism of photocatalytic process from nanomaterials

factored in when selecting the light source. The mechanistic basis of common photocatalytic set-up is shown in Fig. 10. As revealed, photocatalytic process is triggered when a nanoparticle (metal NPs or semiconductor NPs) absorbs light energy, equal or greater than its band gap. This led to the formation of hole (h^+) and (e^-) arising from the promotion of free electrons from the valence to the conduction band. The electron released is used for the conversion of O_2 to superoxide ($O_2.-$). Hydroxyl radical ($OH^{\cdot}$) is formed from hydroxyl ion generated from water molecule reaction with e^-/h^+ pair. The presence of ($OH^{\cdot}$) and ($O_2.-$) ensures the degradation of contaminants/pollutants, e.g., dyes [72, 73].

Nanocellulose materials can provide strong supports for nanoparticle deposition and immobilization for enhanced photocatalytic processes. TiO_2, CeO_2, and other semi-conductor-based nanomaterials are very popular as nanocatalyst owing to their stability, cost-effectiveness, inertness, non-toxicity, and synthesis simplicity. Though their band gaps are quite high in comparison with other nanomaterials, their high catalytic efficiency would cover up for this limitation. Consequently, TiO_2, especially in its special anatase form, has been well exploited for the design of pragmatic photocatalytic set-up as shown in Table 4.

3.3.3 Nanocellulose Materials/Composites in Contaminants/Pollutants Adsorption

Nanocellulose materials and composites have also found enormous applications in contaminants/pollutants remediation in water/wastewater processing owing to their availability, non-toxic nature, toughness, stability, and in some cases porosity. Different groups of pollutants, ranging from pharmaceuticals (tetracycline, amoxicillin), organics, heavy metals (Ag, Au, Hg, Cd), textile dyes, pesticides, etc., are notorious for their persistence and high toxicity load. The capacity of nanocellulose

Table 4 Summarized works of photocatalyst application in pollutant/contaminants degradation in aqueous environment

Photocatalysts	Synthesis strategy	Contaminants/pollutants degraded	Light source	Catalytic efficiency/re-use number	References
Nanocellulose/TiO_2 composites	Ultrasonic impregnation-TiO_2 were mixed with NC aqueous solution and subjected to ultrasonication, then oven-dried	Endocrine disruptor (Mefenamic acid)	450W Mercury lamp	NA/5	Rathod et al. [74]
CNC/TiO_2 NRs/AuNCs	Sol–gel approach	Rhodamine B (RhB)	Solar light simulator	–	Nair et al. [75]
Fe- ZnO/NC	In situ synthesis	Methylene blue MB	250 W high-pressure Mercury lamp	98.84%/	Farahani et al. [76]
Anatase-TiO_2 cellulose nanofiber	1 mL of tetrabutyl titanate and 5 mL of ethanol, were used as reaction solution with 5 h at 55 °C	MO	500 W ultraviolet lamp	99.72% in 30 min	Liu et al. [77]
Anatase-TiO_2 NFC	$TiCl_4$ mixture with NFC solution under stirring. It was then mixed with ammonium per sulfate and HCl for 2 h at 70 °C	MO	36 W UV lamp	95.7% in 60 min	Xiao et al. [78]

(continued)

Table 4 (continued)

Photocatalysts	Synthesis strategy	Contaminants/pollutants degraded	Light source	Catalytic efficiency/re-use number	References
MCC/ZnO composite	Hydrothermal synthesis	MB	UV irradiation (power of 6 W)	93.3%/5 cycles	Zuo et al. [79]
ZnO/NC composite	Heating Zinc salt with NC solution at 90 °C for an hour	MB	UV lamp	Kapp = 0.1174 h^{-1}	Lefatshe et al. [80]
CdS/MoS_2/Montmorillonite on TOCN support	Solvothermal synthesis	Tetracycline	50 W LED lamp	70.5%/5	Yue et al. [81]
CeO_2/TiO_2/ NCC composite	Hydrolysis precipitation	RhB, Cr^{6+} and MO	350 W Xenon lamp	–	Sun et al.[82]

NRs = Nanorod; AuNCs = Gold nanocrystals; NA = Not available; NFC = Nano fibrillated cellulose; TiCl4 = Tin tetra chloride; kapp = Apparent rate constant: TOCN = TEMPO oxidized cellulose nanofiber; CdS = Cadmium sulphide; MOS2 = Molybdenum di sulphide; CeO2 = Cerium oxide

materials/composites in adsorbing these toxic pollutants have received huge scientific attention. They are processed into different shapes and morphologies to increase their long-term durability, adsorption capacity, and re-usability, while also providing simplicity for operationality and ease of handling. Common shapes include hydrogels, aerogels, microgels, and membranes. Hydrogels are 3-dimensional (3D) polymers network, with huge capacity for water absorption in their polymeric networks. Nanocellulose hydrogels contain high hydrophilic groups, which confer capacity for 3D polymeric network formation on exposure to water. They can swell up from between 60 and 80 times on immersion in water. Hydrogels of different functionalities are synthesized and tagged—homopolymers, copolymers, semi-interpenetrating network, and self-assembling peptide systems [83]. Recently, Ren et al. fabricated a multifunctional hydrogel for the adsorption and detection of Cr^{6+}, using cellulose nanofibers obtained via TEMPO oxidation of wood pulp [84]. The hydrogel was impregnated with silver nanoclusters (AgNCs), to impart detection capacity on the nanocomposite. The adsorbent demonstrated maximum adsorption capacity of 418.5 mg/g for Cr^{6+}, while also responding to Cr^{6+} fluorescent detection within the range 0–6 mg/L.

Aerogels on the other hand are 3D polymeric network, with solvent replacement with air, unlike water in hydrogel. They also have numerous pore structures which confer higher absorption/ swelling capacity on them, in comparison with hydrogels. A compressible aerogel was fabricated for the adsorption of Cu^{2+} as investigated by Mo et al. [85]. The nanocomposite was prepared from a TEMPO-oxidized cellulose nanofiber, mix with carboxymethyl cellulose. The mixed polymers were then modified with branched polyethyleneimine, through electrostatic interaction. The adsorbent was responsive to Cu^{2+} adsorption study using a Langmuir adsorption equation with capacity of 452.49 mg/g.

Generally, the adsorption studies are fitted into appropriate equilibrium adsorption isotherms, to obtain the sorption parameters. The commonly applied adsorption isotherms include Langmuir model, Freundlich model, Temkin model, and D-R model [86].

Microgels are another form of adsorbent, made up of micro-meter-sized colloidal particles with tremendous swelling property in water. Jin et al. [87] fabricated a functional microgel for the adsorption of anionic dyes (Congo red and reactive light yellow), in aqueous solution, based on nanocellulose and amphoteric polyvinylamine (PVAm). The adsorption study was carried out at acidic condition to facilitate the protonation of the amino groups in PVAm to improve interaction with the dyes.

Membrane-based substrates are equally used in the design of adsorbents. They are made from tough inorganic materials such as ceramics, metals, and zeolites. They are mostly the most preferred for water treatment involving seawater, desalination, and wastewater treatment plant adsorbents. Recent reviews from Norfarhana et al. [88] have done justice to membrane-based adsorbents designed for wastewater purification.

Another common adsorbent design is the gel beads form. Li et al. [89] reported the fabrication of a mesoporous gel bead adsorbent for the Cu^{2+} and Pb^{2+} in aqueous solution using nanocellulose/sodium alginate (SA)/carboxymethyl-chitosan (CMC)

gel beads aerogel, using simple strategy, of mixing the constituents together in water, then sonicated for complete mixing. The mixture was drop wisely injected in $CaCl_2$ for gel bead formation. The adsorption capacity reached 154.32 456.62 mg/g for Cu^{2+} and Pb^{2+}, respectively. Adsorbent in the form of film, through the simple but effective solution casting method, is also popular. A chitosan-based adsorbent film, impregnated with nanocellulose, was investigated for the adsorption of Cu^{2+} in solution [90]. Chitosan, poly (vinyl pyrrolidone) (PVP), β-cyclodextrin (β-CD), and nanocellulose (NC) were blended and then cast on a surface to form film. The influence of NC on the microstructural and adsorption capacity of the prepared adsorbent was confirmed using different analytical techniques.

Adsorbent fabrication in the form nanofibrous membrane through electrospinning has gained wide acceptance over the years and thus will be fully discussed.

3.4 Nanocellulose Materials/Composites in Electrospinning for Sustainable Fabrication of Processable Nanofibrous Membranes

The movement of fluids under the influence of electrostatic force was first observed by William Gilbert, a personal physician to Queen Elizabeth 1 of England. In 1600, other scientific investigations led to the discovery of electric and electricity. Electrospinning technique however gained prominence in the nineteenth century [91]. In the last past decades, this technique has gained huge traction in the scientific community, with enormous volumes of works continuously churned out yearly. The wide acceptability of the technique may be understood from its simplicity, pocket-friendliness, operational simplicity, adaptability, and durability. Figure 11 shows a simple electrospinning set-up. The viscous polymeric solution inside a syringe, under the influence of an external applied voltage, can be activated and forcefully ejected as thin fibers, which are collected on a collector. During the polymer droplet movement, the solvent in the droplet is rapidly evaporated, then solidifies, and is collected as nanofibers on the collector. The distance between the syringe nozzle tip and the collector is called tip-to-collector distance or tcd. It is one of the most important parameters that affect the property of the electrospun fiber.

Other equally important factors include the viscosity of the polymer solution in the syringe, flow rate applied, the applied voltage (whether direct or alternating current source, DA/AC), and environmental conditions such as humidity and temperature [93]. Nanocellulose materials in combination with other polymers (biopolymers and synthetic polymers) present a versatile bio-based material for the electrospinning technique to generate nanofibrous materials with wide-ranging applications. Electrospun nanocellulose materials mediated fabrication of nanofibrous materials have found applications in biomedicine such as tissues regeneration, in food industries, for the shelf-life extension and food packaging, in adsorbent fabrication for water and

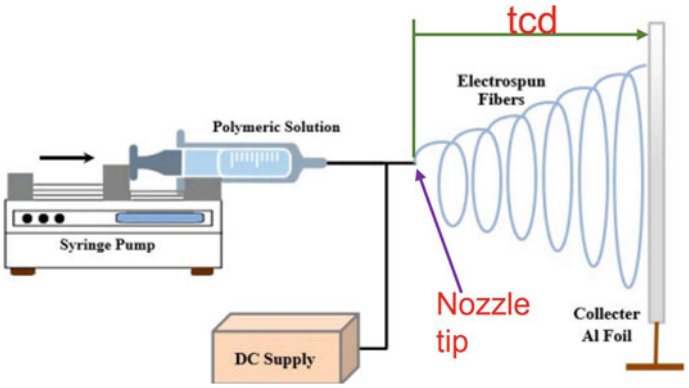

Fig. 11 Schematic illustration of common electrospinning set-up. *Republished with permission from* [92]. Copyright 2016

wastewater treatment, and in analytical detection of contaminants. This wide-ranging application is summarized in Table 5.

3.5 Nanocellulose Materials in Composite with Other Synthetic/Biopolymers for Film Packaging Materials Fabrication, Toward Food Preservation and Safety

The use of plastics (petroleum source) for packaging and other diverse applications had resulted in the destruction of human environment aesthetics, through humongous debris littering the environment. It is claimed that about 4.8–12.7 million tons of plastics found its way to the oceans on a yearly basis, equated to about full baggage full of wastes dumped into the ocean for every minute [103]. Plastics are non-biodegradable and are the precursors of microplastics, a major environmental challenge of the twenty-first century [104]. They are produced from smaller repeating units, called monomers, through polymerization process. Their high resistance to different environmental conditions and their cheap production cost create a booming market with about 4.9 billion metric tons produced in 2015 alone [105]. Plastic alternative is the only way to go, if we are to stem the tide of plastic production and its attendant impact. The use of environmentally friendly materials has been proposed as worthy and reliable prospect. Bio-based materials are biodegradable, abundant in nature, non-toxic and can be processed into different materials of interest to meet human demand. One of the major uses of plastic is in packaging. The use of environmentally sustainable materials in packaging especially food-based products has progressed with excitement and hope. Nanocellulose materials as bio-based resources have been drafted and explored tremendously for the fabrication of food packaging materials. Food packaging materials are imbued with bioactive materials and other addictive to impart

Table 5 Nanocellulose based nanofibrous membrane for wide ranging applications, through electrospinning technique

Nanofiber components	Synthesis strategy	Application	Fiber diameter (nm)	Comment	References
rCNF	Electrospun cellulose acetate fiber was de-acetylated in NaOH and ethanol solution	Bone tissue engineering	300–600	Potential bone tissue engineering prospect was investigated using some in vitro cell assays on MC3T3-E1 osteoblast cell	Chakraborty et al. [94]
PLA/CNC	CNC was mixed with PLA solution and then spun	Bone substitute investigation	–	Effect of CNC on biocompatibility was investigated, with PLA osteogenicity. Crystalline CNC improved the mechanical and thermal property of composite	Patel et al. [95]
PLA/LAE/ CNC	LAE was incorporated in PLA/CNC solution as antimicrobial bioactive	Active food packaging	130–610	LAE release from the fiber was reduced due to the core–shell architecture of the PLA/CNC nanofibrous membrane, to enhance food preservation	Vidal et al. [96]
CNC/PVA	PVA and CNC aqueous solution were mixed via sonication and were spun	Wound healing application	–	Fabricated PVA/CNC mat was impregnated with antimicrobial peptide for improved antimicrobial property	Teixeira et al. [97]
Chitosan-PEO/TEMPO-oxidized cellulose (TOC)	Solutions of chitosan, PEO and TOC, were spun	Water filtration, for deactivation of bacterial strains	–	Membrane was supplemented with Cu^{2+} for improved microbial filtrations	Bates et al. [98]

(continued)

Table 5 (continued)

Nanofiber components	Synthesis strategy	Application	Fiber diameter (nm)	Comment	References
BCN/ PCL/GEL	BC was hydrolyzed to its nanocrystal, and a suspension is mixed with PCL and Gel solutions	Glioblastoma tumor investigation	162–409	Fiber diameter increased with increasing BCN content. The composite is non-toxic which facilitated the growth and adhesion of glioblastoma cell	Unal et al. [99]
PA6/CNW/AgNPs	PA6 solution in formic acid was prepared and was combined with CNW and AgNPs	Analytical detection of Pb^{2+} as electronic tongue	–	The influence of CNW and AgNPs was investigated on PA6, by varying the constituents	Teodoro et al. [100]
PVA/CNC	PVA and CNC solution were mixed and spun	Air pollution filter for particulate matter (PM)	–	Efficient absorption capacity for PM and could be easily desorbed through heating at 60 ^{0}C	Zhang et al. [101]
GO/CNF	CNF solution was spun, while the rolling collector was constantly wet with GO solution	Oil/water separation	–	Fiber showed high water flux, with good anti-fouling property for oil–water separation	Ao et al. [102]

rCNF = Regenerated cellulose nanofiber; PLA = Poly (lactic acid); LAE = Ethyl lauroyl arginate; PEO = Polyethylene oxide; BCN = Bacterial cellulose nanocrystals; GEL = Gelatin; PCL = Polycaprolactone; PA6 = Poly amide 6; GO = Graphene oxide

antimicrobial properties against food spoiling bacteria. The impregnation of packaging films with anthocyanins and betacyanins (natural dyes from plants), which a highly pH sensitive, results in the fabrication of packaging films with pH sensitivity and are called intelligent pH-responsive packaging materials.

He et al. [106] reported the fabrication of a pH-intelligent packaging film, comprising PVA and CNC mix with purple cabbage anthocyanins (PCA), for shrimp freshness monitoring. As revealed, the addition of CNC and PCA improved the mechanical, water vapor barrier property, and UV–vis barrier property of the film. The fabricated film responded to pH incremental changes with color transition from reddish/pink to purple, then blue, to green/yellow. Packaging film impregnation with AgNPs or other metal/metal oxides nanoparticles owe their importance to their high antimicrobial properties. However, the debate on the possibility of nanoparticles leaching from the packaging material is still being subjected to rigorous suspicion among scientists. Wu et al. [107] investigated the use of TEMPO-oxidized nanocellulose (TCN), grape seed extract and grape seed extract-reduced TCN/AgNPs film for improved antimicrobial packaging film. The TCN matrix provided strong support base for the AgNPs immobilization, as confirmed from the low AgNPs release profile from the film. Moreover, the film demonstrated good antimicrobial potentials against *E coli* and *S aureus* strains. Other notable nanocellulose-based packaging films reported are summarized in Table 6.

3.6 Nanocellulose Materials in Biomedicine

Nanocellulose materials are reliable substrates/matrix for the immobilization and delivery of important materials for various applications. The mechanical strength and high surface hydroxyl and carboxyl groups also provide surfaces for reactions with bioactive materials. These functional groups can also form strong hydrogen bonds with immobilized materials, which may be beneficial to improving their stability even in high ionic strength tissue environments. Being itself highly biocompatible [116], nanocellulose materials demonstrate excellent compatibility with most cells, without any deleterious damage. This is indeed a key attribute of material substrates for most biomedical applications. As stated earlier, nanocellulose materials provide excellent surfaces for drugs and bioactive materials encapsulation and onward delivery. For instance, Atila et al. [117] investigated the delivery of vitamin C and E on a pullulan hydrogel immobilized onto bacterial cellulose (BC), through cross-linking, for wound healing application. The presence of BC and pullulan provided double layers which can facilitate the release of vitamins C and E for wound healing processes. Nanocellulose materials are also efficient for the delivery of drugs, metabolites, and active biological molecules of immense applications. For example, Ning et al. [118] reported an efficacious platform for the delivery of anti-cancer drug (paclitaxel, PTX), using a PDA-Py-CNC-AG composite hydrogel, comprising AG (agarose), PDA (polydopamine), and Py-CNC (pyrene fluorophore labeled nanocellulose) system, as shown in Fig. 12. The PDA-modified layer on the

Table 6 Nanocellulose based packaging/intelligent packaging films reported from literature

Packaging materials	Fabrication strategy	Applications	Comments	References
Lignin/CNC	Lignin was extracted from Argan Nutshell, with further modification with epichlorohydrin. CNC was then added to the lignin solution	Food shelf-life extension, through UV protection, for red cabbage	Good film tensile strength, with excellent UV light protection capacity	Halloub eet al. [108]
WG/CNC/TiO_2	Different concentrations of CNC and TiO_2 were injected into WG solution and then cast	Active food packaging	Effect of addition of CNC and TiO_2 was investigated, with increased tensile strength and water resistance	El-Wakil et al. [109]
Alginate/carrageenan/CNC with shellac	Solution of the polymers was prepared and mixed, with shellac addition for improved food protection property	Storage time extension of chicken breast and tomato cherry	Shellac addition to the film increased the storage time for tomato cherry, while the mechanical property of the film was enhanced with composite	Zhang et al. [110]
PVA/NC/AgNPs	NC and AgNPs were added to PVA solution under different ratios	Antimicrobial packaging	Improved tensile strength because of NC addition, while AgNPs improved the antimicrobial potency against *E coli* and *S aureus* strains	Sarwar et al. [111]

(continued)

Table 6 (continued)

Packaging materials	Fabrication strategy	Applications	Comments	References
Hemicellulose/pectin/NC	Aqueous solution mixing of components using sorbitol as plasticizer	Packaging for fatty foods	Hemicellulose/pectin ratio modulated the physical property of film, while CN composite helped in encapsulation of polyphenol	Mugwagwa et al. [112]
CMF/PVA	CMF was injected into PVA solution, at varying ratios	Thermally stable material for packaging	Good mechanical property film was obtained with high thermal stability property	Zhang et al. [113]
Modified CNF/PLA/Chitosan	PLA was dissolved in dichloromethane and then mixed with CNF, which was cast in chitosan solution	Food packaging	Modified CNF increased the film hydrophilicity and its mechanical property	Niu et al. [114]
TOCNFs/(CPNIPAM-AM)	TOCNFs was added at varying concentration in (CPNIPAM-AM) matrix. Natamycin was added to profile its delivery	Fruit packaging	Increased antimicrobial property of film with reliable mechanical strength	Shaghaleh et al. [115]

WG = Wheat gluten; PVA = Poly (vinyl alcohol), NC = Nanocellulose; CMF = Cellulose micro-nanofibril; CNF = Cellulose nanofibril
PLA = Poly (lactic acid); TOCNFs = TEMPO-oxidized cellulose nanofibril; (CPNIPAM-AM) = cationic-modified poly (Nisopropyl acrylamide-co-acrylamide)

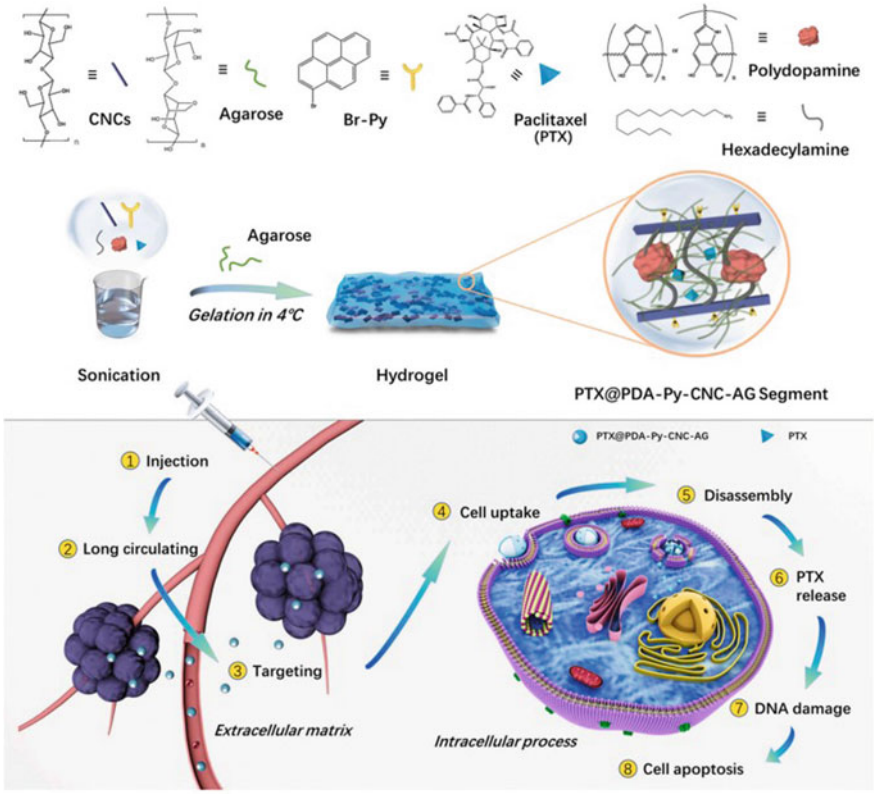

Fig. 12 Schematics of anti-cancer drug delivery paclitaxel, based on PDA-Py-CNC-AG composite hydrogel. *Republished with permission from* [118]. Copyright 2021, Elsevier

hydrogel provided good binding sites for the anti-cancer drug loading. As shown, the design is imbued with high loading efficiency from the extracellular to the intracellular components, where sustained release of PTX was activated for inducing DNA damage and cell apoptosis.

Finally, nanocellulose materials also find application in tissue regeneration. Huang et al. [119] investigated AuNPs on BC hydrogel for bone tissue regeneration. The presence of AuNPs was to impart osteogenic property to the composite, through in situ fermentation procedure, which facilitated the differentiation of human bone marrow-obtained mesenchymal cells. For other notable applications of nanocellulose materials in biomedicine, reviews from Shi et al. [120] and that from Lin and Dufresne [116] are recommended.

4 Conclusion

In this chapter, we have elucidated the properties of different nanocellulose materials, with their common synthesis strategies. Cellulose as a bio-based natural resource holds great promise to ameliorating the negative impacts of synthetic materials applied in diverse human endeavors. Unrivaled as the most abundant natural resources on earth, cellulose will continue to attract huge interest from the scientific community, from now forward and in the future. In this write-up, we have discussed the various applications of nanocellulose materials and their various composites with emphasis on their emulsifying property for Pickering emulsion formulation and stabilization, and their composites with MNPs toward antimicrobial and anti-fungal activity. We also discussed nanocellulose applications in water purification and contaminants reduction through catalysis, photocatalytic process, and adsorption of pollutants and in composites with other polymers for the fabrication of highly reliable nanofibrous materials, through electrospinning technique. We finally wrap it up with nanocellulose applications in the biomedical sector, with their roles in wound healing, drug delivery, and medical implant functions.

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Potential Technologies to Develop Cellulose Beads and Microspheres

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Abstract Consumers, food packaging, and pharmaceutical industry are increasingly demanding products made of raw materials obtained from renewable and sustainable resources that are biodegradable, non-petroleum based, carbon neutral, and have low environmental, health and safety risks. Cellulose macro- and nanofibers are attractive biopolymers of almost inexhaustible quantity, obtained from wood, hemp, cotton, linen, etc., have been expansively used as engineering materials for thousands of years and their use continues today in the fabrication of advanced pharmaceuticals. Cellulose is a lightweight and biodegradable material with outstanding strength, stiffness, and hydrophilic in nature has been rigorously investigated as a reinforcing component in design of various drug carriers including composite, beads, and microspheres. Moreover, polysaccharides fabricated into hydrophilic matrices remain popular biomaterials for controlled or sustained release oral and targeted drug delivery systems among them most extensively modified cellulose used are hydroxypropylmethyl cellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, etc. Additionally, microcrystalline cellulose, sodium carboxymethyl cellulose, ethyl cellulose, oxycellulose, ethyl hydroxyethyl cellulose, and cellulose were obtained

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from plant sources explored by food and pharmaceuticals manufacturers. Microspheres and beads are orally modified in multiple unit dosage forms, however, fabrication of these drug carriers has always been a more effective therapeutic alternative to synthetic non-biodegradable excipients. This chapter summarizes an overview of the processing structure property perspective on the recent advances in synthetic and natural cellulose and their derivatized form with emphasized application in the development of beads and microsphere.

Keywords Cellulose · Cellulose derivative · Beads · Microspheres · Textile valorized cellulose · Packaging

Abbreviations

GIT	Gastrointestinal tract
NCMC	Nano carboxymethyl cellulose
G	Standard gravity
g	Gram
g cm^{-3} g	Per cubic centimeter
h	Hour
K	Kelvin
M	Molar, mol dm^{-3}
M	Meter
m^2g^{-1}	Square meter per gram
min	Minute
mol	Mole, ~6.022 × 1023
s^{-1}	Reciprocal seconds
V	Volt
W	Watt
–COOH	Carboxylic acid group
μ_	Micro, 10^{-6}
ACB	Anionic cellulose bead
AG	Anionic group
AGU	Anhydroglucose unit
API	Active pharmaceutical ingredient
CMC	Carboxymethyl cellulose
CO_2	Carbon dioxide
DMS	Trans-4-[4-(Dimethyl-amino)styryl]-1-methylpyridinium iodide
DPν	Viscosity average degree of polymerization
DS	Degree of substitution
DSC	Differential scanning calorimeter
EC	Ethyl cellulose
FTIR	Fourier transform infrared spectrometer
HEMA	Poly(hydroxyethyl methacrylate)

HPC	Hydroxypropyl cellulose
HPMC	Hydroxypropyl methylcellulose
Wt	Weight
UDP	Uridinediphosphate
THF	Tetrahydrofuran
DMF	Dimethylformamide
DMI	1,3-Dimethyl-2-imidazolidinone
DMA	Dimethylacetal
CNF	Cellulose nanofibril
CNC	Cellulose nanocomposites
MS	Molar substitution
FDA	Food and Drug Administration
LCST	L*ower Critical Solution Temperature*
NaCMC	Sodium carboxymethylcellulose
NaCl	Sodium chloride
US EPA	United States Environmental Protection Agency
L	Liter
g/L	Gram per liter
nm	Nanometer
rpm	Revolution per minute
L/min	Liter per minute
%	Percentage

1 Introduction to Cellulose and Fibers

Anselme Payen, a French chemist, described a tough fibrous solid isolated through acids and ammonia treatment of various plant tissues, followed by processing in pressing with water, alcohol, and ether in 1838 [1]. Furthermore, an elemental analysis technique was used to identify the chemical formula, which was $C_6H_{10}O_5$, and starch to see the isomerism. In a report on Payen's studies, the French academy first adopted the name "cellulose" for this plant element in 1839 [2]. Generally, wood, cotton, and other natural fibers are utilized as an energy source, construction materials, and clothing thousands of years before the discovery of the "sugar of the plant cell wall". Cellulose materials have influenced human civilization since the Egyptian era.

1.1 History

About 150 years of chemical raw material is used for the processing of cellulose. It was proved in 1870 by the Hyatt Manufacturing Company that chemical modification

of cellulose might yield new materials on an industrial scale by producing cellulose nitrate by reaction with nitric acid [3, 4]. With this understanding came a rise in the usage of synthetic wood cellulose fibers for textiles and technological items. The viscose process is the most significant large-scale technological process in fiber manufacturing today [5]. The non-digestible component of the plant cell wall, dietary fiber has undergone multiple definition modifications since its discovery by Hipsley [6]. The dietetic and chemical industries describe dietary fiber as a marketing topic [6]. Later, Kay in 1982 defined it as dietary fiber, a widespread component of plant meals, which is an insoluble substance resistant to human digestive enzymes [7]. Moreover, "dietary fiber consists of plant cells that are resistant to hydrolysis (digestion) by human alimentary enzymes", according to Trowell et al. [8]. In addition, dietary fiber is enzyme-resistant cellulose, non-cellulosic polysaccharides including hemicellulose, pectic compounds, gums, mucilage, and lignin. High-fiber diets, such as cereals, nuts, fruits, and vegetables, lessen the risk of many diseases. Dietary fiber benefits pastries, drinks, beverages, and animal goods.

These dietary components are characterized by solubility in a buffer at a given pH and/or fermentability in an in vitro system using human digestive enzymes. Dietary fibers are classified as water-insoluble/less fermented (cellulose, hemicellulose, lignin) or water-soluble/well fermented (pectin, gums, mucilage). Figure 1 illustrates dietary fiber solubility and fermentability [9].

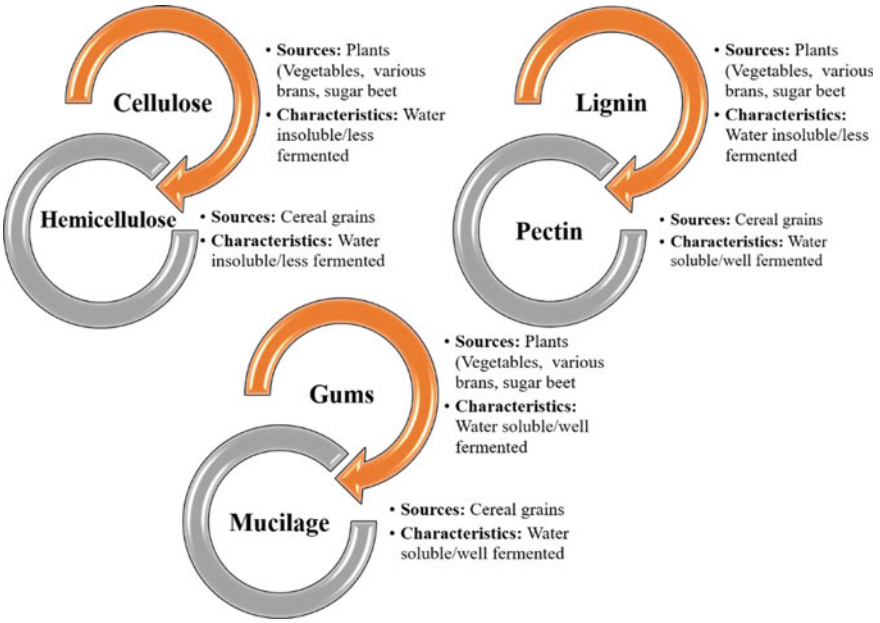

Fig. 1 Water solubility and fermentability classifications of dietary fiber components

1.2 Cellulose

Cellulose is the main component of plant stiff cell walls, a linear polysaccharide polymer with many glucose units. The acetal linkage is beta, unlike starch. This particular variation in acetal connections affects human digestion. Humans cannot digest cellulose due to a lack of enzymes that break down the beta acetal bonds. Indigestible cellulose is the fiber that keeps the intestines moving smoothly [10]. The breakdown of cellulose in GIT requires symbiotic bacteria that live in the digestive tracts of animals including cows, horses, sheep, goats, and termites. They contain the enzymes needed to break down or hydrolyze cellulose, whereas mammals, including termites, do not. Direct digestion of cellulose is impossible for any vertebrate. Despite its inability to digest, cellulose is widely used in construction, explosives, and fabrication of paper, textiles, and films. Cellulose is made up of long polymer chains of glucose units linked by beta acetal linkages. Beta acetal linkages connect C # 1 of one glucose to C # 4 of the next glucose [11].

Polysaccharide-based cellulose has an unusual structure and properties. The highly functionalized linear stiff-chain homopolymer is hydrophilic, chiral, biodegradable, chemically modifiable, and produces semi-crystalline fibers.

Cotton fiber is 95% cellulose, while wood-derived cellulose is just 50% pure. Photosynthesis helps plants to produce cellulose in their leaves; the yearly output of cellulose in nature is 10^{11} to 10^{12} tonnes. Cellulose and its derivatives are commonly used as excipients in traditional pharmaceuticals due to their easy functionalization. Cellulose and its derivatives have returned in medicinal delivery. High Tg, compatibility with a wide spectrum of therapeutic chemicals, and exceptional self-assembly in micro/nanostructures. The above-mentioned desirable qualities and the fast progress of nanotechnology in the last two decades enable the design and development of cellulose-based drug carrier systems [12]. Cellulose derivatives are a viable alternative to pure cellulose since they dissolve in water and organic solvents. Low cost, biocompatibility, and biodegradability make them suitable for biomedical and bioanalysis applications. Enhanced cellulose derivatives-based composites were used to make films and membranes for osseointegration, hemodialysis, biosensors, smart textile fibers, tissue engineering scaffolds, hydrogels, and nanoparticles for drug delivery [13].

Cellulose-based microspheres have several medication deliveries uses. After activating carboxyl groups, cellulose microspheres can establish covalent bonds with enzymes. Improved pH tolerance, thermal stability, simple recovery, and reusability make emulsified microspheres attractive enzyme carriers [14].

This chapter explains the structure and chemistry of cellulose, as well as the uses of innovative cellulose esters and ethers for coatings, films, membranes, construction materials, drilling operations, medications, and foods. Moreover, new cellulose technologies including eco-friendly fibers, bacterial biomaterials, and in vitro synthesis have been explored [15].

1.3 Hemicellulose

After removing water-soluble and pectic polysaccharides, these are cell wall polysaccharides solubilized by aqueous alkali. They have backbones of glucose units with 1, 4 glucosidic connections, although they are smaller, have more sugars, and are generally branched than cellulose [7]. They are largely made up of xylose, with traces of galactose, mannose, arabinose, and other sugars thrown in for good measure [9].

1.4 Lignin

It is a complicated random polymer made up of approximately 40 oxygenated phenylpropane units, including coniferyl, sinapyl, and p-coumaryl alcohols, that has gone through a difficult dehydrogenative polymerization process. However, the molecular weight and methoxyl content of lignins differ. Lignin is particularly inert due to strong intramolecular bonding, which includes carbon to carbon bonds. Lignin outperforms all other naturally occurring polymers in terms of resistance [9, 16–18].

1.5 Pectin

Pectic polysaccharides include D-galacturonic acid which are plant cell wall structural components and intercellular cement. These soluble pectic polysaccharides are excellent hypoglycaemic due retardation in stomach emptying and small intestinal transit [19]. In addition, the free water-soluble pectin is completely digestible by colonic bacteria.

1.6 Gums and Mucilage

Plant gums and fibers are generated in specialized secretory cells and are not cell wall components [20]. These are branching polysaccharides that gel either binding with water or organic molecules. Moreover, gums are sticky exudates generated by trauma (gum arabic). They are mostly guar gum and gum arabic. Guar gum is a galactomannan found in Cyamopsis tetragonolobus seeds (guar). Partial enzymatic hydrolysis yields a soluble dietary fiber. This fiber's physiological properties are consistent with soluble fibers, while gum arabic is a complex arabinogalactan polysaccharide with a glycoprotein. Mucilage is secreted into the endosperm of seeds to keep them hydrated.

The study shows that the initial phase in cellulose breakdown is the creation of insoluble hydrocellulose or oxycellulose, which decreases Fehling's solution and

is unstable and reactive. Decomposition of hydrocellulose, oxycellulose, or hemicellulose creates a mucilaginous compound with a greater copper number than hydro-, oxy-, or hemicellulose, which cements parchment paper. Too much breakdown produces sugars or acids from mucilage.

2 Microspheres and Beads

The new medicine delivery technology relies on several nanotechnologies such as carriers-based drug delivery, microspheres, and beads. A well-designed controlled/sustained drug delivery system may alleviate some of the issues of predictable treatment and increase the therapeutic effectiveness of a specific medicine. A therapeutic chemical may be delivered to the treatment site in several ways, some of which include prolonged controlled release. The active moiety incorporated within microspheres is evenly distributed throughout the particle's interior structure, which is a polymer matrix. Modifying this method ensures that the medication will reach its intended location with high specificity and that it will remain at the right concentration for the duration of the study without causing any side effects. Free-flowing particles made from biodegradable synthetic polymers are known as microspheres [21].

The size range of microspheres is from 0.1 to 200 μm [22]. Not only were microspheres studied for drug release prolongation, but they were also used to target life-threatening diseases such as anticancer treatments directly to tumors. To ensure that the particle surface area is consistent and predictable, spherical microparticles are utilized. The medicine in a microsphere is positioned at the particle's center and is surrounded by a special polymeric membrane. There will be a central role of microspheres in novel drug delivery in future, especially in diseased cell sorting, diagnostics, genetic materials, targeted and effective drug delivery [23].

2.1 Classification of Microspheres

Bio-adhesive microspheres: These microspheres hold mucoadhesive properties that enable the drug-coated polymer to cling to the targeted organ, prolonging drug delivery to the sick spot [24]. Magnetic microspheres include magnetic particles that may target medicine delivery. Diagnostic and drug delivery microspheres are available. These magnetic particles may direct drugs to target tissue or organs. They are often used to heat tumor tissue using magnets [25]. Floating microspheres release drugs into the stomach. The bulk density of drug-loaded microspheres should be lower than gastric liquid so they may float, prolonging drug release [26].

Radioactive microspheres: Particles (10–30 microns) are injected directly into veins related to the targeted organ or tissue. Radioactive particles emit and wave. Preparing microspheres vary in their size, route of administration, crosslinking time, release time, etc. [27, 28].

3 Sources, Chemistry, and Property of Cellulose and Fibers

Cellulose is a polysaccharide composed of D-glucose linked via β-1,4 glycosidic linkages and is a prospective raw ingredient in the manufacture of key compounds, such as cellulosic-ethanol, hydrocarbons, and polymer precursors Fig. 2a. Hydrogen atoms in cellulose occupy the axial position, while hydroxyl groups occupy the equatorial position. These equatorial hydroxyl groups may establish hydrogen bonds with their close neighbors, allowing cellulose to crystallize [29].

3.1 Cellulose and Fibers from Plants Resources

As stated, several plant sources are employed to extract cellulose for nanowhisker research, however, their compositions vary (Table 1) [30–37]. In most instances, the plants employed for cellulose nanowhiskers extraction are inappropriate for industrial usages, such as maize straw waste, banana crop leftovers, wood chips, and

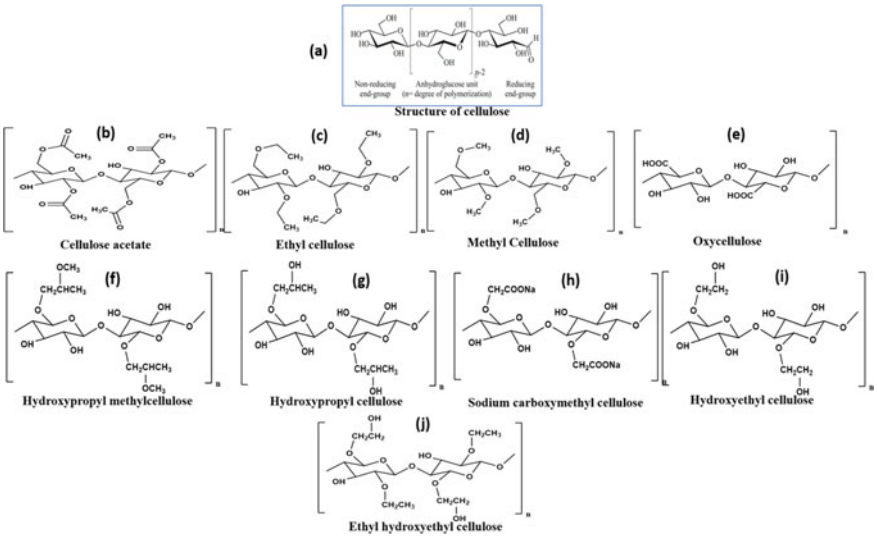

Fig. 2 Schematic representation of the chemical structure of cellulose and its derivatives

Table 1 Sources of cellulose and fibers [27–34]

Fiber source	Origin	% Cellulose	Fiber source	Origin	% Cellulose
Banana	Leaf	60.0–65.0	Maize straw	Straw	28.0–44.0
Coir	Fruit	32.0–43.0	Nettle	Bast	53.0–86.0
Cork bark	Leaf	12.0–25.0	Rice husk	Straw	25.0–35.0
Corn cob	Stalk	33.7–41.2	Softwood	Stem	42.0–50.0
Cotton	Seed	82.7–95.0	Sugar cane	Stem	32.9–50.0
Curaua	Leaf	63.4–73.6	Sisal	Leaf	60.0–73.0
Flax	Stem	64.0–84.0	Wheat straw	Stalk	30.0–35.0
Hardwood	Stem	39.0–50.0	Hemp	Stem	67.0–78.0
Jute	Bast	51.0–78.0	Ramie	Bast	67.0–99.0

wheat straw. The usage of non-reusable garbage is growing, therefore, contemporary research focuses on environmental challenges and biomaterials.

3.2 Rice Husk Cellulose

This variation in the chemical composition of rice husk samples may result from the paddy variety, sample preparation, meteorological and geographical conditions, and technique of analysis [38]. Rice husk that has not been processed has a brown color, but after being treated with an alkaline solution, it takes on a color that is between brown and orange. After being processed, the bleached material is easily distinguishable from the original and looks to be completely white. Chemical treatment of rice husks removes non-cellulosic components and contaminants such hemicelluloses, lignin, wax, and pectin. The finished product's white color indicates it is nearly pure cellulosic material that matched with elemental quantification. Rice husk fibers originally had 35% cellulose, 33% hemicelluloses, 23% lignin, and 25% silica ash. The alkali treatment efficiently removed hemicellulose, reducing it from 33 to 12 wt%. Hemicellulose was effectively eliminated by the alkali treatment, which led it to reduce from 33 to 12 wt%. Alkali treatment eliminated nearly all silica, but lignin concentration remained almost unchanged. Hemicellulose and lignin were completely eliminated during the bleaching process, leaving nearly pure cellulose fibers with a 96% purity level [39].

The structural composition of the native RH and extracted cellulose can be quantified using infrared spectroscopy. Moreover, FTIR spectra indicate how treatment affects the functional groups of RH fibers. The absorbance peaks of lignocellulosic components such as lignin and cellulose were typical in the 1800–400 cm^{-1} range. The band at 1720 cm^{-1} ascribed as C = O stretching from hemicellulose's carbonyl and uronic ester groups. The peak related with the lignin structure was discovered near 1600 cm^{-1}, pertaining to the aromatic C = C stretching, and disappeared following

bleaching, indicating full breakdown and elimination of the lignin complex [40]. The FTIR spectrum of rice husk cellulose also reveals a broad absorption peak at 3330–3500 cm^{-1}, indicating stretching of O–H group. The C–H stretching vibrations are responsible for the absorption peak at 2800–2900 cm^{-1}. The absorption band at 1030–1180 cm^{-1} corresponds to a C–O–C asymmetrical bridge identified as a cellulose 1,4-β-glycoside bond [41, 42]. The peak found around 1300 cm^{-1} in the spectrum of the treated rice sample is characteristic of a change in the symmetry of the C–H group [39, 42].

3.3 Bacterial Cellulose

Various bacteria from the genera Acanthamoeba, Acetobacter, and Achromobacter spp. generate cellulose, which is a promising path to high-DP pure cellulose (Fig. 3). Bacterial cellulose possesses a remarkable ultrafine network structure with excellent crystallinity and a substantial amount of stable water incorporated into the structure.

A cellulose-synthesizing complex is associated with the surface pores of the bacterium *Acetobacter xylinum*, responsible for the production of cellulose. This originates between the outer membrane of the bacteria and the membrane surrounding the cytoplasm. The enzyme cellulose synthase has been thought to be the most critical in this process. In the -1,4-glucan polymerization, glucose-1-phosphate is converted to uridine diphosphoglucose (UDP-glucose) by the activity of UDP-glucose pyrophosphorylase [43].

Acetic acid bacteria, particularly *Gluconacetobacterxylinum* generate cellulose and at the air–liquid interface, create a thick and leather-like pellicle when cultivated in an appropriate statically incubated surface culture media [43]. Bacterial cellulose has the same molecular structure as those produced by plants. Bacterial cellulose's excellent mechanical strength, crystallinity, water holding capacity, and porosity

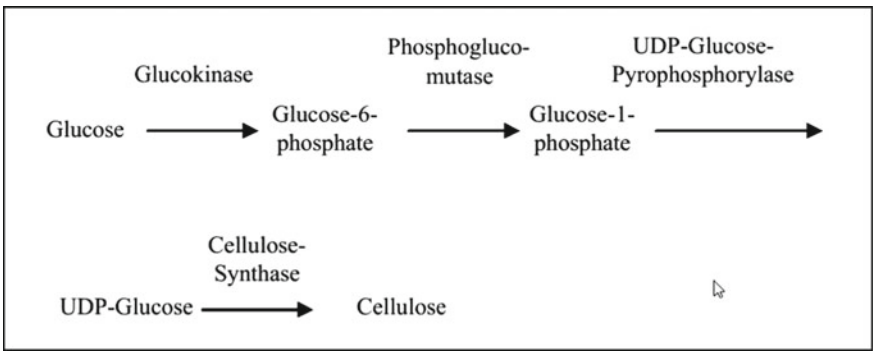

Fig. 3 Proposed biochemical path for cellulose synthesis in Acetobacter xylinum by Cannon RE and Anderson SM [44]

make it a useful biomaterial. Bacterial cellulose is extremely pure, including no lignin, hemicelluloses, or other biogenic by products.

3.4 Cellulose Acetate

Cellulose acetate (CA) is the acetate ester of cellulose, Fig. 2b. It is also known as xylonite or acetylated cellulose. The introduction of acetyl groups causes a dramatic shift in the biostability of the compound. Despite this, cellulose acetate is a biodegradable polymer that has gained widespread recognition [45]. Each anhydroglucose molecule in cellulose may be esterified (such as acetate substitution). Cellulose acetate is produced by esterifying the 2-, 3-, and 6-hydroxyl groups of cellulose's anhydroglucose units (AGUs) with acetic anhydride in the presence of acetic acid as a solvent and concentrated sulfuric acid as an esterification catalyst [46].

Traditionally, CA synthesized from sugarcane bagasse, polysaccharide, and valonia cell using acetic acid and acetic anhydride with sulfuric acid as a catalyst. However, in recent years, cellulose acetate synthesis has included the utilization of ionic liquids at room temperature without the use of catalyst [47]. CA characteristics such as viscosity and solubility are intimately associated with the individual degree of substitution throughout the cellulose chains [48]. Numerous industrial applications for cellulose acetate include coatings, textile fibers, consumer goods, composites, filtration membranes, laminates, and medicinal products [49].

Das and a co-worker reported that compared to native cellulose, CA indicates downshift in OH stretching band at 3322 cm^{-1}, increased C = O stretching band at 1751 cm^{-1}, increased C–H bending vibration at 1369 cm^{-1}, and a higher C-O stretching vibration at 1220 cm^{-1}. The presence of (C–O) ester bonds at 1751 cm^{-1}, CH bond in $OCOCH_3$ group at 1369 cm^{-1}, and C–O stretching band at 1220 cm^{-1} reveal evidence of acetylation [29].

3.5 Ethyl Cellulose

Ethyl cellulose (EC) is structurally the same as cellulose and cellulose acetate, with the exception that part of the hydroxyl (OH) functional groups on cellulose is replaced with ethoxy groups (OCH_2CH_3) as presented in Fig. 2c. Therefore, EC is a derivative of partially O-ethylated cellulose ether. EC is produced via Williamson ether synthesis involving the reaction of alkali cellulose with ethyl chloride [50]. The synthesis of EC required higher temperature, alkalinity, and reaction time. Commercially, cellulose is alkalized with 50% sodium hydroxide and reacted with ethyl chloride at 50 °C for 10 to 20 h. The end product EC has nearly identical partial DS(Et) values at O_2 and O_6, but a lower DS(Et) value at O3 [51]. During a reaction, ethoxyl groups can be substituted for up to 44.5 percent, which is lower than the maximum theoretical value of 3.0. Within above range, four ethyoxyl types are distinguished:

EC-G-type (44.5–45.5%), K-type (45.5–46.8%), N-type (47.5–49.0%), and T-type (49.5–50.0%). Furthermore, due to the breakdown of H-bonds and structural regularity maintained by the ethyl groups, EC is soluble in water at low DS(Et). However, EC with high DS(Et) represents insolubility in water, whereas solubility in non-polar solvents such as aromatic hydrocarbons. Therefore, the solubility of EC is inversely proportional to DS (Et) [51, 52]. The substitution level or ethoxyl content has a direct effect on the EC's characteristics. If EC's DS is increased to 2.8, an insoluble material is produced, showing the relationship between solid-state packing defects and cellulose derivative solubility [52]. EC is often used as a binder, taste masker, coating agent, and matrix tablet for modified release in pharmaceutical formulations. The N and T ethyoxyl types having low viscosity grades are commonly utilized as binders in concentrations between 2 and 10% [53]. In oral pharmaceutical formulations, EC is often used as a coating material for granules and tablets which regulate the drug-release rate and disguise unpleasant tastes [52]. Trivedi and a co-worker reported the FTIR of EC, indicating the C-H stretching peak was between 2974 and 2869 cm^{-1}. Other prominent peaks at 1091 cm^{-1} and 1373 cm^{-1} include C–O–C stretching and C–H bending. Similarly at 3485 cm^{-1}, the –OH stretching vibration was noted [54].

3.6 Methylcellulose

Methylcellulose (MC) is a methyl ester derivative of cellulose which consist of 27.5–31.5% of methoxy groups, (Fig. 2d). The methoxyl content of a standard MC structure with a DS value of 1.75 is 29.1 wt%. [52]. Commercially, MC is manufactured by reacting alkali-treated cellulose with methyl chloride as an electrophile in a Williamson ether synthesis. MC, like CMC, can be manufactured using a dry process or a slurry process. The diluents like ethylene glycol, dimethyl ether, or toluene are commonly used for the slurry method [51]. DS has a significant impact on MC water solubility (Me). When DS (Me) ranges between 0.1 and 1.1, the polymer swells and becomes water-soluble when DS (Me) is between 1.4 and 2.0. However, at DS (Me) 2.1, it loses its water solubility. MC with a DS of 1.5 is highly soluble in both cold and hot water, as well as in polar aprotic solvents including DMI, DMF, and DMAc. It is insoluble in solvents of lower polarity, like acetone, THF, and alcohols, which restricts the number of formulation methods for drug delivery [51].

Thermo-reversible gelation is an intriguing characteristic of aqueous MC solutions. They become gelled when heated to around 55 °C and then dissolve again when cooled. It seems to be widely acknowledged that hydrophobic interactions between methyl groups are the primary source of gelation in MC solutions [55]. In the pharmaceutical industry, MC has been utilized as a binder, thickener, stabilizer, film former, and suspending agent. Because of the amphiphilicity and solubility of MC in viscous aqueous solutions, it also has been used as a polymeric carrier in controlled release formulations. MC can form water-soluble films with low non-polar gas (oxygen and carbon) dioxide permeability. These can be used as film dosage forms or taste-masking coatings. The plastic flow and wetting qualities of low molecular weight

MC make it a versatile binder. It produces granulations and tablets that are easily compressed and have a moderate degree of hardness [51, 53].

The significant difference between MC and cellulose samples is the reduction in intensity and change in profile for the 3400 cm^{-1} band, which is due to the stretching of cellulose's OH bond (hydroxyl groups) during the methylation procedure. Moreover, the existence of cellulose's CH and CH_2 groups and MC's CH_3 group increases C–H stretching bands by approximately 2900 cm^{-1} in the IR spectra of MC. The presence of C–O–C bonds at about 1100 cm^{-1} indicates cellulose ethers. The effectiveness of the methylation process is confirmed by the shift in the band profile of O–H and C–H stretching bands [56].

3.7 Oxycellulose

Oxycellulose is also called oxidized celluloses, which are water-insoluble compounds formed by oxidation of cellulose (Fig. 2e). The commonly used oxidants are hydrogen peroxide, peracetic acid, nitrogen dioxide, chlorine dioxide, permanganate, persulfates, hypochlorous acid, or hypohalites. Depending on the use of different reaction conditions and types of oxidant, oxidized celluloses in addition to the OH group may also have aldehyde, ketone, and/or carboxylic groups [57]. In chloroform, N_2O_4 partially oxidizes cellulose's primarily alcoholic groups to carboxyl groups. The primary alcoholic groups of water-soluble polysaccharides like starch can also be converted to carboxyl groups in the presence of an oxidizing agent at pH 9–11 by the 2,2,6,6-tetramethylpiperi-dine-1-oxyl (TEMP) radical with excellent yields and selectivity [58].

3.8 Hydroxypropyl Methylcellulose

Hydroxypropyl methylcellulose also called as hypromellose is a partly O-methylated and O-(2-hydroxy-propylated) ether derivative of cellulose (Fig. 2f). Here, a secondary hydroxyl group is introduced via the hydroxypropyl group; this group can be etherified during HPMC synthesis, leading to further chain extension. HPMC is utilized in solid oral dosage forms as a binder, controlled release matrix, and film coating agent [59]. It is commonly used to make hydrophilic matrix tablets because it forms a homogenous, strong, viscous gel layer quickly, limiting matrix disintegration, and regulating drug release. It commercially exists in the varying DS and MS variants. The USP/NF and other compendia have designated different substitution types of HPMC with a four-digit number, where the first two digits indicate % content of the more methoxy group and the second two digits indicate % content of the more hydroxypropoxy group like hypromellose 2910, and hypromellose 2208. These differences in the molecular weight and ratios of methoxy and hydroxypropoxyl substitutions influence the properties of the polymer, including solubility, swelling, diffusion, and

drug-release rate. In modified release formulations, hypromellose 2208 (K grade) and 2910 (E grade) are most often used [52].

3.9 Hydroxypropyl Cellulose

Hydroxypropyl cellulose (HPC) is an ether of cellulose in which part of the hydroxyl groups on the cellulose backbone has been replaced with hydroxypropyl groups (Fig. 2g). Each additional hydroxypropyl group further adds a secondary hydroxyl group that are etherified during HPC production, leading to chain elongation. When this occurred, the molar substitution (MS) refers to a number of moles of hydroxypropyl groups per anhydroglucose ring is greater than DS. Therefore, HPC requires an MS of roughly 4 to reduce cellulose crystallinity and improve water solubility. HPC is hydrophobic and has an LCST of 45 ºC owing to its high hydroxypropylation content (about 70%). HPC is easily soluble at temperatures below the LCST; however, above the LCST, HPC is insoluble. HPC is commonly utilized as a film coating agent, binder, and extrusion aid in solid oral dosage forms. There are six different commercially available HPC viscosity grades, with average molecular weights ranging from 80,000 to 1,150,000 Da [52].

HPC is synthesized by heating alkali cellulose with propylene oxide under high pressure, which causes the cellulose rings to open nucleophilically. As a consequence of this, hydroxypropyl (HP) substituents are produced, which nearly exclusively consist of alkali salts of secondary hydroxyl groups. These produced anions are now ready to react with propylene oxide. The alkoxyl group on the side chain can react with additional molecules of propylene oxide (PO) to produce oligo (propylene oxide) side chains, and each of these side chains can have more than one combined PO. Below 38 ºC, commercial HPC with an MS range of 3.0–4.0 is water-soluble, but it maintains outstanding thermal gelation capability when combined with MC121 and other cellulose ethers. As a consequence of thermal gelation, HPC becomes insoluble in water at temperatures above 45 ºC [51].

3.10 Carboxymethyl Cellulose and Sodium Carboxymethyl Cellulose

Sodium carboxymethyl cellulose (NaCMC) is an anionic carboxymethyl ether derivative of cellulose (Fig. 2 h). NaCMC is a commercially available polyanionic derivative of cellulose that is physiologically inert and water-soluble, the polyelectrolyte has a significant affinity for water but has low solubility in organic solvents. If the polyelectrolyte is pre-dissolved in water, it can resist adding water-miscible solvents without precipitation. NaCMC is synthesized by reaction of alkali-treated cellulose with chloroacetic acid. Glycolic acid is produced as a byproduct when Cl^-

is displaced from chloroacetic acid during Williamson ether synthesis, along with NaCl [57]. The slurry method is used for the production of commercial NaCMC. The first step is to dissolve the cellulose in a solution of water, alcohol, and NaOH. Finally, the solvent moves the chloroacetate and the dissolved base to the hydroxyl groups of the cellulose. Hydrogen bonds are broken, and the hydroxyl groups are activated, moving cellulose further to etherification. Another way is to use a dry process, which starts with the preparation of alkali cellulose and then adding monochloroacetate while it is still solid. Bhandari et al. proposed a new approach for the synthesis of NaCMC, reactive extrusion, which is a continuous, time-saving procedure that takes less than two minutes and reduces solvent usage [60].

In pharmaceutical formulations, NaCMC is utilized as a thickener, disintegration agent, film-forming agent, bioadhesive material, and stabilizer. Croscarmellose, or cross-linked NaCMC, is commonly employed as a super disintegrant in tablet and capsule formulations. NaCMC has good film-forming capabilities and is commercially available at 700 K molecular weight [51]. Owing to its viscosity-increasing and gelling properties, it is used in oral, injectable, ophthalmic, and topical pharmaceuticals [52, 53].

3.10.1 Hydroxyethyl Cellulose

Hydroxyethyl cellulose (HEC) is a partially substituted polyhydroxyethyl ether derivative of cellulose (Fig. 2i). In ocular and topical formulations, it is utilized as a viscosity modifying agent, binder, and controlled release matrix former. Additionally, in solid dosage forms, it is utilized as a film coating agent. Likewise, HPC synthesis, each hydroxyethyl group added during the preparation of HEC adds a secondary hydroxyl group which is etherified further, tending to the additional expansion of the chain. Therefore, the molar substitution corresponding to a number of moles of hydroxyethyl groups per anhydroglucose ring will be greater than the DS. HEC dissolves quickly in cold or hot water to form a clear, transparent aqueous solution that doesn't gel or precipitate even when boiled. HEC is available in various grades with viscosity and dynamic shear (DS) corresponding to 90,000–1,300,000 Da average molecular weights [52].

3.10.2 Ethyl Hydroxyethyl Cellulose

Ethyl hydroxyethyl cellulose (EHEC) is cellulose derivative with ethyl and hydroxyethyl groups attached to the anhydroglucose units via ether linkages (Fig. 2j). EHEC is synthesized by reaction of alkali treated cellulose with ethylene oxide and ethyl chloride. It is insoluble in both boiling water and ethanol and swells in water which forms a translucent to an opalescent colloidal solution. The Food and Drug approved the usage of EHEC as an inert ingredient in non-food pesticides as well as an emulsifier, stabilizer, cathartic, and thickening in food. In addition to its usage as a binding

and stabilizing agent, additionally EHEC is also used as a protective colloid in pharmaceuticals. Moreover, EHEC is distinguished from other cellulose derivatives by the presence of a cloud point. At higher temperatures, EHEC becomes less soluble. The polymer chains dehydrate and precipitate cellulose ether. This initially increases turbidity (clouding), followed by a substantial fall in viscosity during the continuous phase.

3.10.3 Microcrystalline Cellulose

Microcrystalline cellulose (MCC) is a cellulose derivative that has been partially depolymerized using mineral acids. MCC is a common filler-binder used mostly in the direct compression method of tablet manufacturing. Its superior binding characteristics as a dry binder have led to its widespread application in direct compression. Its superior binding characteristics as a dry binder have led to its widespread application in direct compression. It also works as a disintegrant, diluent, and lubricant in direct compression formulation. In addition to its usage as a diluent, MCC is a common capsule and sphere filler [61]. MCC was traditionally made from wood pulp, bamboo, and viscose rayon. In addition, to newspaper waste, bagasse, corncobs, and rice straw, attempts have been made to manufacture MCC from fast-growing plants such as Pinus roxburghii and Sesbania sesban. The reaction of acid with cellulose results in the disruption of the β-1,4-glycoside bond and the breakage of the acetal linkage. This causes the chain to break down and the polymerization degree to drop [62].

4 Valorization of Waste Textile-Based Cellulose

In recent years, textile waste has gained significant attention among researcher and commercial manufacturers. Population growth causes demand for textiles and garments to surpass supply [63, 64]. In 2015, 93.2% of Hong Kong's textile waste was landfilled and 6.8% was recycled domestically or overseas. Secondhand overseas commerce and cremation are major textile recycling possibilities [65, 66]. In the existing inefficient, linear system, substantial material wasted in landfilling or incineration is inescapable, causing damage to environment and social harm, while textile manufacturers also emit greenhouse gases. Cellulosic material has been widely studied for biorefinery biofuels and chemicals [67–69]. Cotton, a cellulosic-rich substance with high polymerization and crystallinity, makes about 35–40% of textile waste [70, 71]. In most cotton waste bioprocesses, enzymatic hydrolysis converts cellulose to fermentable sugars [72]. The expense of enzymes hinders the commercialization of these technologies.

In the management and preparation of textile waste, several types of cotton and polyester blend textile waste given by H&M (Hennes and Mauritz, Far East) were employed as raw feedstock [63]. Pure cotton, PET, and 99/1% cotton/elastane jeans

were also used. Textile scraps were ground into tiny pieces (0.8 0.8 cm^2) before pre-treatment and fungal fermentation. Dr. Shao-Yuan Leu from HKPU performed pre-treatment. The ground textiles were soaked in 12% NaOH and 7% urea, then frozen for 6 h. After thawing, samples were rinsed with DI water until pH was 7.0 [73, 74].

Global textile fiber production is in million tonnes and solid waste too in million tonnes. Cotton makes up 24% of all textile fibers [75]. It is the main ingredient of textile and is the most popular cloth item. A cloth recycling is important to the textile and fashion industries. Cotton is mostly made of cellulose, a biocompatible, biodegradable, and renewable natural polymer used in many sectors [76]. Cellulose is used for energy storage, medicinal delivery, and tissue engineering [77–79]. Cotton is a cellulose-rich feedstock; therefore, discarded textiles can be converted into value-added cellulose products [80].

Cellulose beads, sometimes called microspheres, are an excellent product. It is a versatile, high-performance material [81–83]. Cellulose beads are absorbents for heavy metal ions and enzymes in environmental remediation and the food sector [84, 85]. Cellulose beads are a suitable filler material because of their spherical form [82]. Cellulose beads offer stronger mechanical rigidity than silica-based beads and a simpler manufacturing procedure than synthetic polymer-based beads [81, 86, 87].

Preparing cellulose beads involves dissolving, spheronizing, and coagulating [83].

Drying beads under appropriate circumstances preserves their porosity [88]. Size of cellulose beads ranges from micrometers to millimeters, depending on shape [89–91]. Spherical droplets are regenerated in an anti-solvent bath. This procedure forms porous cellulose beads by exchanging the dissolving solvent and anti-solvent [92]. The interior porous structure or morphology of cellulose beads is significant for applications such as medication loading [93, 94].

Most cellulose aerogels are fibrous or spherical. The fibrous morphology consists of three-dimensional fiber-like entanglements inherited from the cellulose polymer chain [95, 96]. Changing polymer content, dissolving solvent/anti-solvent, and cellulose functionalization can affect morphology [89, 97, 98].

5 Processing and Biodegradation of Cellulose and Fibers

Biodegradability makes cellulose fibers an eco-friendly textile material, which simplifies their management and treatment in the waste stream. Since soil bacteria destroy cellulose polymers, cellulose-based items may be composted. More than 60% of post-consumer textile waste is still dumped in landfills or illicit dumping (US EPA 2021). Biodegradable cellulose fibers aren't always desirable in textiles. Mold and fiber deterioration may lower the value of biodegradable materials when exposed to the right circumstances. Biodegradability is incompatible with antibacterial activity, a desirable feature of medicinal cellulose fibers. Antimicrobial drugs are needed to protect users against harmful bacteria. However, antimicrobial drugs

damage bacteria that biodegrade fibers. The creation of cellulose textiles with excellent antibacterial activity throughout use and retained biodegradability at the end of life remains one of the major difficulties in chemical textile finishing.

Antimicrobial finishes differ in chemical composition, particle size, and efficacy. Nano-finishing textiles using metal and metal oxide nanoparticles (NPs) as an alternative to antimicrobial finishing have gained interest. Small concentrations of highly reactive nanoparticles may give remarkable antibacterial activity [72–76]. Ag, Cu, CuO, Cu_2O, TiO_2, and ZnO-NPs and their mixtures are good textile antimicrobials [77–79]. Antimicrobial action of metal and metal oxide NPs is complex and attributed to release of metal cations and NPs from textile surface and generation of reactive oxygen species (ROS) under UV light. Chemical and morphological characteristics, concentration, photocatalytic effectiveness to produce ROS, and environmental circumstances impact NP antimicrobial efficacy.

6 Pharmaceutical Technologies Involved in the Fabrication of Cellulose-Based Products

Choosing the method depends on the polymer (Table 2), the drug, and many formulations and technological factors, such as particle size requirements. There are many procedures for making microspheres from hydrophobic and hydrophilic polymers. Preparing microspheres choosing the method depends on the polymer, the drug, and many formulations and technological factors, such as particle size requirements.

Preparing cellulose-based products is of growing interest to scientists in chemistry, chemical engineering, biochemistry, and other related fields [99–102]. Polysaccharides have outstanding mechanical and chemical characteristics and are abundant, biocompatible, and sustainable [103–106]. Chemical alteration makes cellulose hydrophilic, hydrophobic, anionic, or cationic [107–109]. In several cutting-edge applications, including chromatography, solid supported synthesis, protein immobilization, and delayed drug release, cellulose beads are spherical particles with sizes in the micro- to millimeter range. The making of cellulose beads has been done in a variety of ways during the last several decades, including using various solvents, shaping processes, and technological equipment for large-scale manufacturing. By adding various chemical functions or mixing cellulose with organic and inorganic chemicals, functional materials for particular uses have been created. Additionally, there are commercial cellulose beads with specific qualities on the market [8, 110, 111].

Table 2 Various polymers sued for the development of microspheres and beads [72–75]

Natural and modified polymers	Synthetic polymers
Agarose, chitosan, gelatin, hyaluronic acid, carrageenan, pectin, sodium alginate, cellulose derivatives CMC, thiolated CMC, Na CMC, hydroxyethylcellulose, HPC, HPMC, methylcellulose, methylhydroxyethylcellulose	Polymers are based on poly(meth)acrylic acid. Carbopol, polycarbophil, polyacrylic acid, polyacrylates, copolymer of acrylic acid and PEG, copolymer of methylvinyl ether and methacrylic acid, Poly-2-hydroxyethylmethacrylate, copolymer of acrylic acid and ethylhexylacrylate, polymethacrylate, polyalkylcyanoacrylates:- polyisobutylcyanoacrylate, polyisohexylcyanoacrylate. Others Poly-N-2-hydroxypropylmethacrylamide, polyhydroxyethylene, PVA, PVP, thiolated polymers
Polymer with surface charge Aminodextran, dimethylaminoethyldextran, chitosan, quaternized chitosan,chitosan-EDTA, PAC, carbopol, polycarbophil, pectin, sodium alginate, Na CMC, CMC	Polymer with no surface charge Hydroxyethylated starch, HPC, PEG, PVA, PVP
Water-soluble cellulose derivatives CMC, thiolated CMC, Na CMC, hydroxyethylcellulose, HPC, HPMC, methylcellulose, methylhydroxyethylcellulose Others Poly-N-2-hydroxypropylmethacrylamide, polyhydroxyethylene, PVA, PVP, thiolated polymers. Ethylcellulose, polycarbophil	Water-insoluble cellulose derivatives: Polymers based on poly(meth)acrylic acid carbopol, polycarbophil, polyacrylic acid, polyacrylates, copolymer of acrylic acid and PEG, copolymer of methylvinyl ether and methacrylic acid, poly-2-hydroxyethylmethacrylate, copolymer of acrylic acid and Ethylhexylacrylate, polymethacrylate, polyalkylcyanoacrylates:- polyisobutylcyanoacrylate, polyisohexylcyanoacrylate
CMC = carboxymethylcellulose; HPMC = hydroxypropylmethylcellulose; PEG = polyethylene glycol; PVA = polyvinyl alcohol; PVP = polyvinylpyrrolidone; HEC = hydroxyethylcellulose; HPC = hydroxypropylcellulose; PAA = polyacrylic acid; EDTA = ethylenediaminetetraacetate	

6.1 Preparation Technologies

Round cellulose beads were first mentioned in the literature in 1951 [112]. Dropping a viscous solution by hand into an aqueous coagulation bath produced cellulose pellets. Since then, several other solvents and methods have been devised to produce cellulose beads with diameters ranging from 10 μ to 4 mm (Fig. 4). Beads are made by (i) dissolving cellulose (or a cellulose derivative), (ii) shaping a polysaccharide solution into spherical particles, and (iii) subjecting the particles to a sol gel transition and hardening them into beads. Multiple post- and pre-treatments may be necessary to get the desired results.

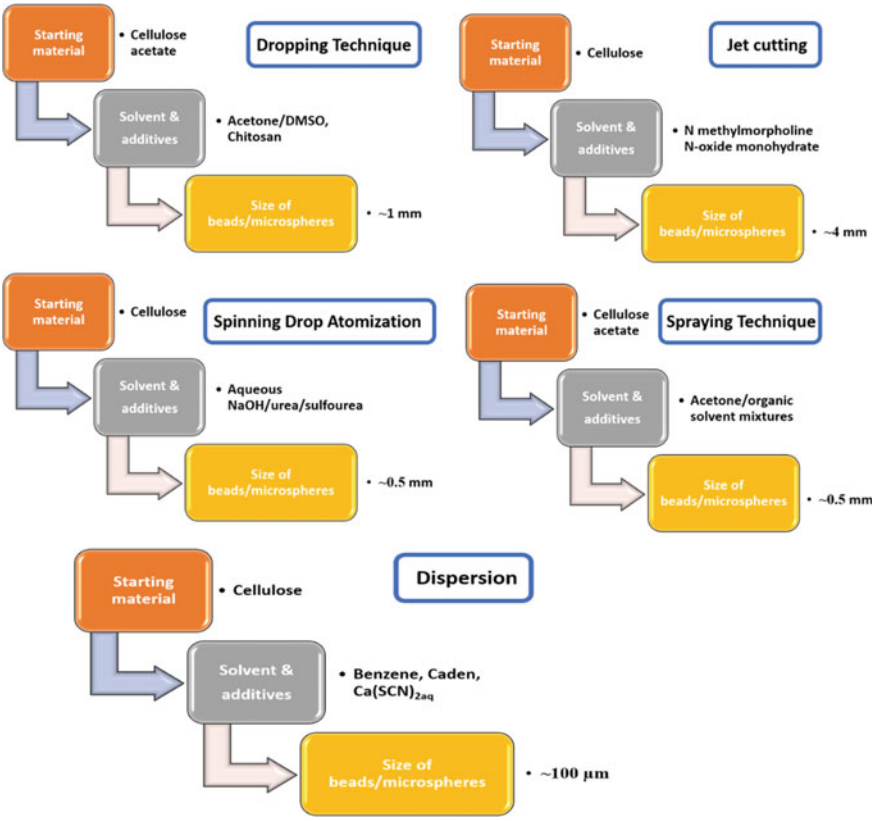

Fig. 4 Preparation technologies of microspheres and beads [83]

Cellulose and its derivatives are employed in drug delivery agents including beads and microspheres. In 2021, Zafar et al. produced chitosan and cellulose microspheres for nasal domperidone administration using solvent evaporation technique. The microsphers were obtained in spherical shape with 21.12 ± 0.51 m particle size, percent entrapment (84.79 ± 1.39), and percent drug loading (50.68 ± 0.96) with 81.2 ± 6.75% of drug release in 8 h. The in vivo findings demonstrated that the formulation was superior to oral and nasal formulations [113]. Zang and colleagues fabricated porous microspheres from bacterial cellulose and collagen for bone tissue engineering with a pore diameter of 198.5 nm, specific surface area of 123.4 m^2/g, and pore volume of 0.59 cm^3/g [114]. Simei Wu and coworkers developed phosphorylated cellulose microspheres for ciprofloxacin with first-order of release kinetics followed by non-Fickian mechanism. Cytotoxicity makes ciprofloxacin microspheres a perfect carrier for safe drug release [115]. Xiaoxiao Sun and colleagues formulated pH- and magnetism-responsive Fe_3O_4@C/CMC/chitosan microbeads of diclofenac sodium with good encapsulation and pH-sensitive drug release without burst release in GIT [116]. Fan Xie and colleagues fabricated diazepam and itraconazole porous

amorphized dialdehyde cellulose beads by periodate oxidation with drug loading up to 40% and improved drug dissolution [117]. Karzar and colleagues developed carboxymethylated cellulose magnetized nanocrystals beads for pH-sensitive release of dexamethasone, resulting in eco-friendly, smart, magnetically sensitive hydrogel beads. The formulation had increased loading capacity, swelling property, and pH-sensitive drug release [118]. Gholamali and Yadollahi formulated cellulose-based anticancer beads by add mixing CMC, starch, and ZnO nanoparticles (ZnO-NPs), as well as $FeCl_3$. The quantity of drug released and hydrogel swelling depend on CMC, pH, and ZnO nanoparticle concentration. Furthermore, ZnO nanoparticles incorporating CMC/starch beads, longer, and more regulated drug release was discovered [119]. Ankit Shah and colleagues fabricated dopamine-releasing magnetic-non-magnetic cellulose beads. The encapsulation and release kinetics of these beads was studied at pH 7.4. Drug release from microspheres was boosted by 46% in a magnetic field. Cellulose beads are a naturally occurring, biocompatible drug delivery vehicle for long-term, on-demand new-age drug delivery vehicles with high cycle-to-cycle and device-to-device drug release repeatability [120]. The cellulose-based products approved by the FDA are listed in Table 3. Characterization of cellulose microspheres/beads using a variety of physical, chemical, and analytical methods is shown in Fig. 5.

Table 3 Cellulose-based products approved by FDA [121]

Product	Type	Clinical indication/use	Company/agency
Basyc	Vessel implant (tubes)	coronary artery bypass surgery (CABG)	Jenpolymer materials Ltd. & Co
Bio-fill	Wound care system	Burns	Robin goad
Bioprocess	Artificial skin	Burns	Bio-fill® Biotechnologicos
Cellulon	Binder	Pharmaceutical uses, such as in nonwoven constructions	CP Kelcoz
Cellulon PX micro-fibrous cellulose	Suspending agent	Enzymes in a particle-based suspension	CP Kelco
CelMat® MG &CelMat® MG	Protective dressings/jackets	Protection for miners from potential burns	Government of Poland
Dermafill	Wound care dressing	Burns	Fibrocel
Gengiflex	Non-resorbable cellulose	Periodontitis	Biofill Products Biotechnologicos
MTA protective	Biocompatible implant	Injury and wound care	Xylos Corporation
Securian	Tissue reinforcement matrix	Tendon repair	Xylos Corporation

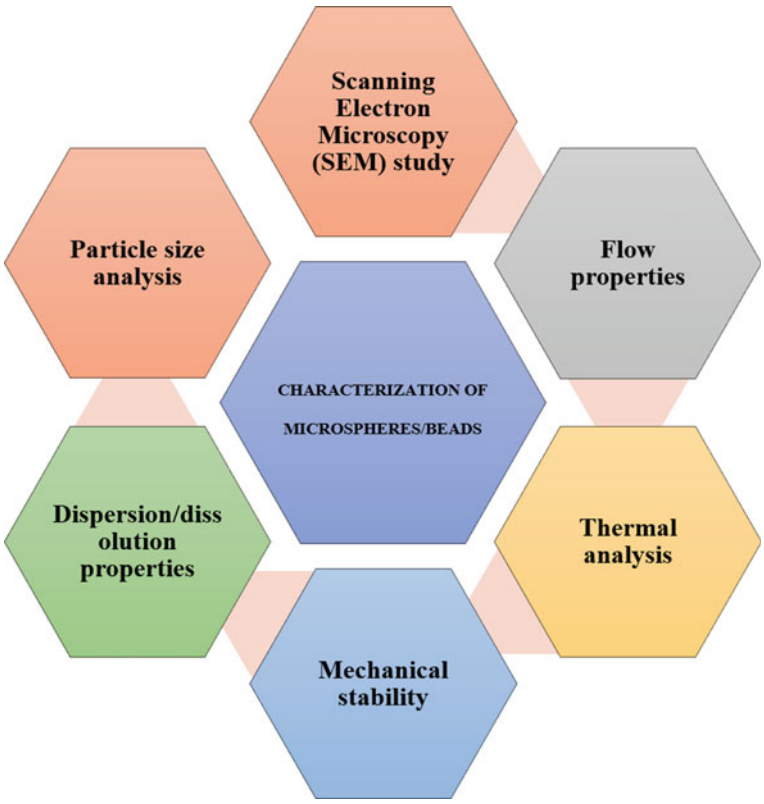

Fig. 5 Various characterization parameters for evaluation of microspheres/beads

7 Applications of Cellulose and Fibers

The impregnation or partial surface dissolution methods are used to make all types of cellulose composites from cellulose sources. Celluloses that are biodegradable and recyclable might be used to replace petroleum-based and biodegradable polymers. Cellulose composites have better mechanical properties and show promise in terms of oxygen permeability. Packaging, aerogels, textiles, and electrical devices can all benefit from all-cellulose composites. Inorganic nanoparticles in all-cellulose composites might have unique functions [122].

7.1 Cellulose-Based Products in Food Preservation and Packaging Applications

The US Product and Drug Administration (FDA) have designated Bacterial Cellulose (BC), a dietary fiber, as a food that is "generally regarded as safe" (GRAS) [123]. Due to its indigestibility by humans, one of BC's key benefits as a food ingredient is its attractiveness for dietetic cuisine [124]. In addition to improving mouth feel, it facilitates intestinal transit (as do other dietary fibers) [125].

A popular dessert from the Philippines called nata-de-coco, which is essentially made from BC grown from coconut water loaded with numerous carbohydrates and amino acids, cut into cubes, and submerged in sugar syrup, has long used BC as the raw material [43]. BC replaces fat in meatballs [126].

BC and BCNC are hydrophilic due to the high density of hydroxyl groups on their surfaces [127]. Hydrophobic interactions result from crystalline organization and extensive hydrogen bonding of chains, making them amphiphilic [128–130].

BC may sustain oil in water (O/W) emulsions (containing 10% olive oil) better than commercial cellulose derivatives (HPMC and CMC) due to the robust network established by the BC fibrils adsorbing oil droplets [131].

BC thickens, gels, and binds water. It increases tofu gel strength, prevents cocoa precipitation in chocolate drinks, and maintains beverage viscosity after heating [132].

Synthetic materials utilized as packaging raw material have several problems. Cellulose is a polysaccharide with several useful features. Using cellulose as a packaging material sounds efficient.

In many applications, natural or biodegradable materials are replacing synthetic polymers. Since the food sector utilizes many plastics, even a slight reduction in materials for every package would reduce polymers and improve solid waste [133]. Biodegradable polymers offer an alternate and partial answer to the challenge of collecting synthetic inert polymer waste [134].

Starch and cellulose are the best-known renewable materials for biopolymers and biodegradable plastics [133, 135]. Weber et al. said the only bio-based food packaging used commercially is cellulose [136].

Environmental difficulties are causing our society to adapt to sustainability. Non-degradable compounds are widespread, therefore, agricultural and forest resources are heavily used. Cellulose's numerous qualities show its potential as a reinforcement. Mechanical properties of cellulose vary.

Cellulose makes up about 94% of cotton and wood (over 50%). Cotton and wood are the main supplies for cellulose products such paper, textiles, construction materials, cardboard, and cellophane, rayon, and cellulose acetate.

Uncoated cellulose films are particularly permeable to water vapor, hence, they are utilized for fresh bread and some sweets. Heat-resistant, heat-sealable, machinable, and printable cellulose films.

Many thermoplastic and thermosetting coatings contain cellulose derivatives. Cellulose esters give fast drying, early hardness, flooding and floating suppression, and crosslinking reactions.

Commonly used cellulose sources, techniques, and applications in the development of microspheres/beads is presented in following Table 4.

Table 4 Cellulose sources, techniques, and impact on size of microspheres/beads

Technique	Active API	Cellulose/fiber	Microspheres/beads size	References
Solvent evaporation technique	Azithromycin	Ethyl acetate, dichloromethane, chloroform	112.546–171.342 μm	[137]
Double emulsification and solvent evaporation	Tretinoin	Ethyl cellulose, light liquid paraffin, span 80	20–150 μm	[138]
Solvent evaporation method	Aceclofenac	Eudragit, ethyl cellulose	47–53 nm	[139]
Emulsion-crosslinking method	Ketorolac tromethamine	Sodium carboxymethyl cellulose (NaCMC)	247–535 μm	[140]
Spray-drying technique	Ketoprofen	Cellulose acetate butyrate	1.50–40.0 μm	[141]
Emulsification and solvent evaporation methods	Nifedipine (NFD) and Verapamil Hydrochlorid	Ethyl cellulose and cellulose acetate	3.36–10.94 μm	[142]
Solvent evaporation method	Nifedipine	Cellulosic polymers	117.17932.14 and 415.529157.10 mm	[143]
Emulsion-solvent evaporation method	Pseudoephedrine HC1	Cellulosic polymers	45–150 pm	[144]
Solvent evaporation technique	Cefpodoxime proxetil	Ethyl cellulose and HPMC	256 μm to 480 μm	[145]
Solvent evaporation method	Theophylline	Cellulose acetate	747 ± 0.6 μm	[146]
Emulsion crosslinking method	Isoniazid	Chitosan and hydroxyethyl cellulose	66–82 μm	[147]
Emulsion-solvent evaporation Method	Metformin hydrochloride	Ethyl cellulose	500 μm	[148]
Oil-in-oil emulsification method	Chlorpheniramine maleate	Ethyl cellulose and cellulose acetate	500–800 μm	[149]
Hydrogel bead formation	Lipase (Enzyme)	Cellulose (Microcrystalline)	2.0–2.4 mm	[150]

7.2 Miscellaneous Pharmaceutical Applications

Roshanak Tarrahi and colleagues created a curcumin-loaded cellulose scaffold. Entrapment efficiency was 83.7% and the swelling ratio was 136%. The smart cellulose-based scaffolds demonstrated excellent antibacterial activity with low toxicity and were a clever, innovative. Anirudhan and colleagues fabricated nanocellulose-based, pH-controlled curcumin drug delivery device with maximized drug loading, pH-based drug release, and applicability against breast cancer [151]. Cellulosic gels have recently gained attention. Making hydrogels frequently involves polymerization using CNC/CNF/MCC or physical/chemical crosslinking of polymer components. Aerogels are created by drying hydrogels and adding air. Their unique structure is used in biomedicine.

8 Conclusions

Beads of varied size and shape from functional cellulose can be used in a wide range of applications. The morphology of this beads depends on the nature of cellulose and manufacturing processed used, simultaneously varied morphology significantly affects their applications. The methods for their manufacture, characterization, and especially chemical modification have advanced continuously over the past decades since they were originally described in this chapter. Cellulose is abundant in nature, biodegradable, and relatively economic and is a promising nano-scale reinforcement material for polymers. Furthermore, the combination of biodegradable cellulose and renewable polymers is particularly attractive from an environmental point of view. Therefore, cellulose can be a potential alternative not only in the fabrication of microspheres and beads but also for the fabrication of another dosage form with excellent biodegradability.

As a result of the considerable attention that innovative polysaccharide solvents are currently receiving in scientific, applied, and business-oriented research, future breakthroughs in the field of functional cellulose beads might be predicted.

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Cellulose-Based Materials for Chromatography and Separation Applications

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Abstract Cellulose-based materials are the current requirements in the area of chromatography for cutting-edge interdisciplinary research work in pharmaceutical industries, research and development, and academic research centers globally. The application of this regenerated cellulose can be used in different chromatographic analysis. Basically, the raw materials are applied for normal phase chromatographic separation. These packing materials are cellulose-based immobilized chiral stationary phases that are further applied in chromatographic separation for chiral racemates. The current work focuses on morphological aspects of different types of regenerated cellulose-based stationary phases utilized for separation of various molecules under different chromatographic techniques. The application of cellulose-based materials is also discussed in detail. The current chapter will be helpful to the scientists and chromatographers, worldwide.

1 Introduction

It is well documented that chromatography is a technique and being used for the identification, separation and purification of the ingredients of a compound. The very first Mikhail Tsvet, a botanist in 1906 in Warsaw (Poland) invented this technique for the separation of leaf pigments into colored bands [1]. The term chromatography chosen from the Greek words khromatos (color); and graphos (write) means to write. Different subchromatographic techniques under the chromatographic wing are being used for the separation, identification and purification of sample mixture even at very

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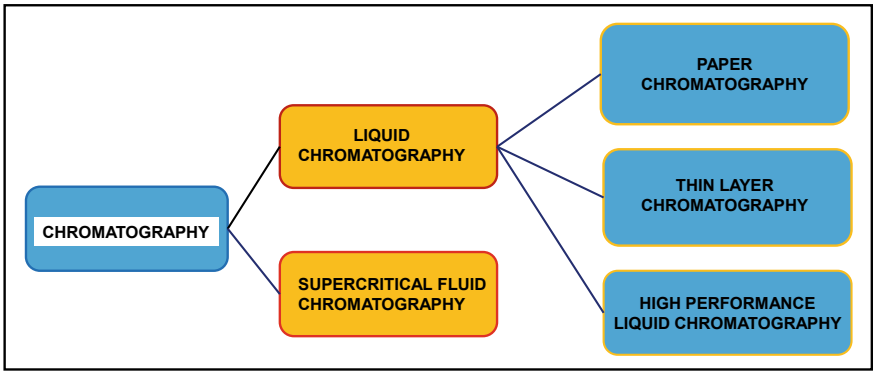


Fig. 1 Schematic representation of chromatographic techniques (cellulose-based)

low concentrations. Currently, various types of chromatographic techniques are in practice for the separation of components mixture. The mechanism of chromatography is based on the distribution of a solute between mobile phase (moving phase) and the stationary phase (fixed phase). The sample (solute) interacted between both mobile and stationary phases based on the distribution of solute and designated by partition (k) or distribution (D) coefficient.

$$K \text{ or } D = \frac{\text{Amount (concentration of solution) in stationary phase}}{\text{Amount (concentration of solute) in mobile phase}}$$

The mobile phase (moving phase) in chromatography is used either a liquid, gas, or a supercritical fluid, while the stationary phase typically a solid matrix or may be a liquid. Further, the chromatographic techniques may be subdivided into diverse names as per phases used and the principles of interaction involved for the separation of compound mixture.

The chromatography based on cellulose application is divided into liquid chromatography (LC) and supercritical fluid chromatography (SFC). The liquid chromatography further divided into three major categories of chromatography techniques that are derived based on mobile phase used such as paper chromatography (PC), thin layer chromatography (TLC) and high-performance liquid chromatography (HPLC). A schematic representation of chromatographic techniques based on cellulose is mentioned in Fig. 1.

2 Liquid Chromatography

The moving phase (mobile phase) can be a mixture of solvents or pure solvent in isocratic (fixed) or gradient ratio that is applied for the separation compounds.

Similarly, the stationary phase (fixed) can be a paper, thin layer, or a packed column of silica, alumina, or cellulose.

2.1 Paper Chromatography

In this chromatographic technique, the stationary phase is a cellulose paper strip, and the mobile phase is a liquid in appropriate composition. About 5μL to 10μL of liquid sample is applied on one cm distance of the strip from bottom side and then allowed to dry in air. This paper from the sample side edge is positioned in a developing chamber containing mobile phase inside. In the developing chamber, the atmosphere is being saturated prior with mobile phase. The mobile phase moves rise to paper because of capillary action and separate the sample spot in its constituents on the cellulose paper strip along the way of solvent front; consequently, a chromatogram is developed on the paper strip. This cellulose paper strip is then removed from developing chamber, and the spots are identified manually or by any appropriate technique (Fig. 2).

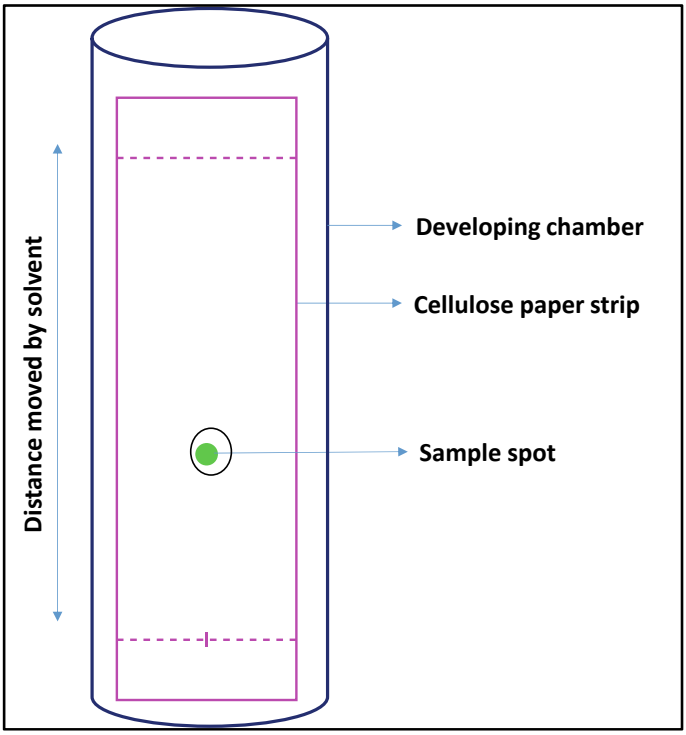


Fig. 2 Pictorial presentation of paper chromatography (cellulose-based)

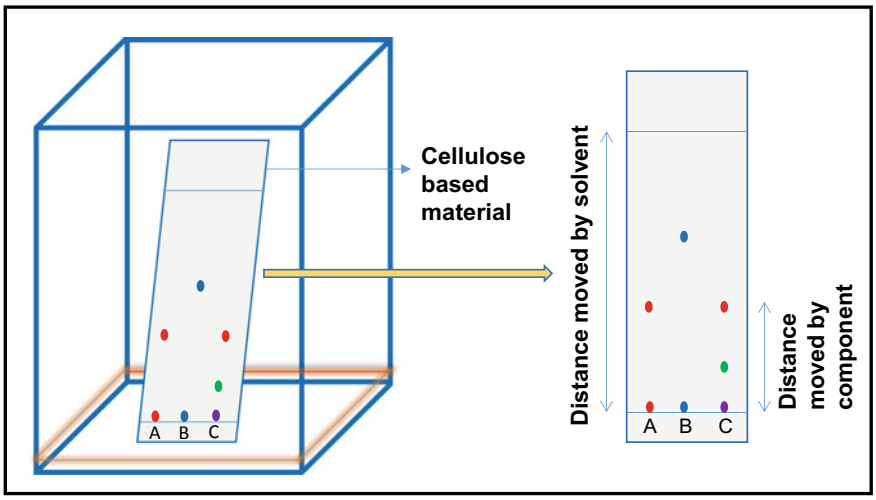


Fig. 3 Pictorial presentation of thin layer chromatography (TLC)

2.2 *Thin Layer Chromatography (TLC)*

TLC is more precise, rapid and reproducible technique. The particles of the TLC plate are smaller and excellent in shape as compared to fibers of papers. Therefore, the resolution in TLC is fine than paper chromatography. TLC has numerous advantages such as low cost, higher sample load and at the same time can be used for number samples. TLC is broadly used in many areas of R&D industries, food, pharmaceuticals and environment. TLC is being in practice for the separation of molecules up to moderate-scale milligram to gram level and for the identification of mobile phase components for scaled-up separation of molecules by column chromatography (CC) (Fig. 3).

In thin layer chromatography or paper chromatography, molecules present in a mixture are identified by their R_f-values (**relative** retention), where:

$$R_f = \frac{\text{Distance travelled by component}}{\text{Distance travelled by solvent front}}$$

2.3 *High-Performance Liquid Chromatography (HPLC)*

It is a well-known fact that high-performance (pressure) liquid chromatography (HPLC) has made a noteworthy contribution in the analysis of a various type of samples. The very first HPLC was introduced in 1964 by Kirkland and Huber [2]. HPLC is considered as the advanced form of column chromatography. The mobile

phase is pumped through the HPLC column, and thus, the chromatographic separation of components is achieved with their retention time. The separated components were being detected by an appropriate detector after moving out from the column. This complete process of HPLC is measured by a computer. The analyst or end user is taking care of all the instrument system along with the sample preparation and placement of prepared samples into the sample tray. After completion of the analysis, the computer generates chromatogram containing other details of the sample, i.e., final analysis report. HPLC columns are accomplished enough to do precise and rapid separation with efficient results and can also be reuse after cleaning and washing properly.

It is a well-known fact that separation by HPLC can be 100 times faster than any other way of conventional liquid chromatography, such as classical gravity column chromatography, in which the separation may take hours or in some cases even days; however, HPLC can offer analysis time of minutes in between 5 and 60 min. HPLC is more appropriate for the analysis of thermally liable and polymeric samples, and all these can be analyzed at ambient temperature (RT) or just above ambient temperature (40–70 °C). HPLC can also be applied for the analysis of research and development samples, natural products, or biological samples. This wide range of unique qualities makes HPLC a significant role in pharmaceutical, pathological, clinical, natural products, forensic and environmental analysis. Therefore, high-performance liquid chromatography is indeed best technique in separation science. The components of HPLC are pump, injector, mobile phase, column, detector, data recorder, etc. which are shown in Figure 4. The data system (computer-based software) also functions as a controller of aforesaid components. All the above modules are connected each other through stainless steel or polyether ether ketone (PEEK) tubing for the smooth flow of mobile phase from reservoir to detector followed by waste. The material of tubing quality of inner surface and its internal diameter (i.d.) have a high impact on HPLC analysis [3]. The HPLC detectors are playing very important role for sample detection. The most widely used HPLC detectors are UV-Vis absorption (UV-Vis), fluorescence (FLR), refractive index (RI), evaporative light scattering (ELS) and mass (MS). UV-Vis and ELS detectors are frequently used in pharmaceutical companies for UV active and UV non-active molecules, separately, respectively. MS detector is generally used for the identification, characterization and quantification of sample (analyte). HPLC is being utilized in more or less in all areas of chemistry, biochemistry, bioanalytical, forensic science, pharmacy and environmental sciences. Some of them are: analysis of drugs and its intermediates, drugs in biological samples, synthetic polymers, environmental pollutants, QC and R&D samples of pharmaceuticals industries, etc. A detailed schematic diagram of HPLC is given in Fig. 4.

The HPLC system functions mainly on two different ways, such as normal phase (NP) and reverse phase (RP), based on mobile and stationary phase (column chemistry) conditions. In normal phase mode, the mobile phase is non-polar solvent mixture such as n-hexane with methanol (MeOH), ethanol (EtOH), isopropyl alcohol (IPA), whereas stationary phase is polar for instance silica, diol, CN, amide, IA, IB,

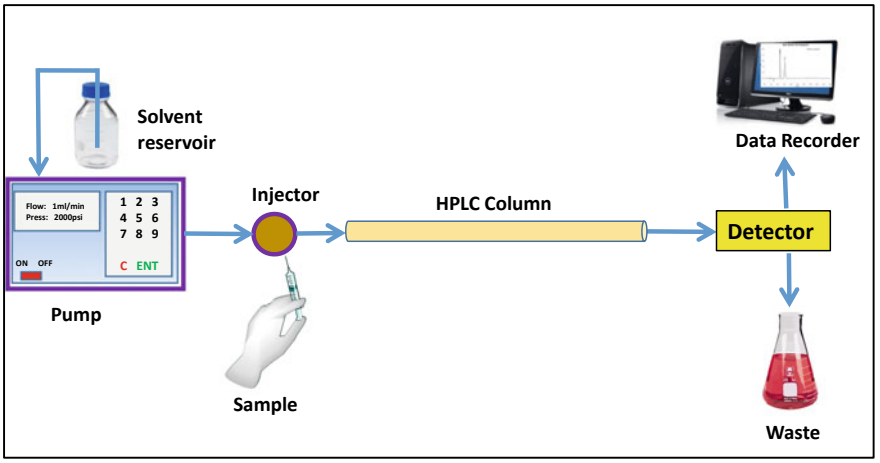


Fig. 4 Schematic diagram of HPLC system

etc. Similarly, in reverse phase mode, mobile phase is polar (mixture of acetonitrile–water, methanol–water or tetrahydrofuran–water), whereas stationary phase is non-polar, for instance, C4, C8, C18, etc. One more mode is HILIC mode (hydrophilic interaction) which is almost similar to normal phase, though used for polar compounds that are not get retained by reverse phase mode. In normal phase, the elution order of analytes takes place based on decreasing order of hydrophobicity, i.e., more hydrophobic first followed by more hydrophilic last eluted. Similarly, in reverse phase, the elution order of analytes is in vice versa.

3 Supercritical Fluid Chromatography (SFC)

HPLC has quite a lot of advantages such as ease of instrumentation handling and varied applications, which make it favorite in the pharmaceutical companies [4–7]. However, some drawbacks are there, for example, long equilibration and analysis time, high-pressure drop, leading high pumping pressure along with use of toxic and environmentally concerned solvents (mobile phases).

Different types of supercritical fluids that may be utilized as mobile phase in chromatography were firstly introduced by Klesper et al. in 1962 [8]. The unique quality of SFC is lower viscosity higher diffusivity, density and solvating power moving ahead to a liquid and gaseous state. These influencing aspects recommend that it persuades lower pressure throughout the column followed by rapid movement during analysis [9–11]. The SFC technique was applied due to its advanced features and uniqueness. It is a constant process of transition among supercritical and liquid states. In SFC, carbon dioxide is used as a mobile phase (eluent) due to its several advantages.

Actually, decrease in temperature and pressure increase the mobility of CO_2 by altering it into a gaseous state and can be simply percolated after application. It is clear that CO_2 is inert, safe and ecofriendly to analysts and humans as well. In light of the above evidences, SFC is well thoughtout as a green technology. These all qualities make us recognize why mixture of CO_2 and a cosolvent is the best eluents for SFC [12–14]. Also, the solvents used in SFC are cheap as compared to organic solvents.

4 Chiral Stationary Phases (Cellulose-Based Materials)

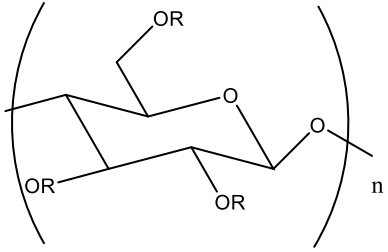
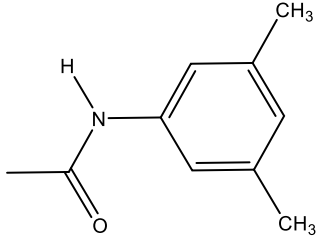
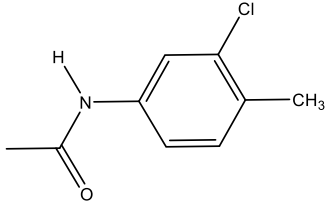
The chromatographic application of regenerated cellulose-based materials is being opted by various manufacturers under different brand names. The morphological aspects of these regenerated cellulosed-based materials can be used either in normal phase or reverse phase chromatographic separations at a time. The mobile phase can be polar in reverse phase such as mixture of acetonitrile–water, methanol–water and tetrahydrofuran–water while non-polar in normal phase such as methanol, ethanol, hexane, heptane and isopropanol. The beauty of aforesaid cellulose-based materials is that it is immobilized chiral stationary phases that can be used in both phases like reverse and normal phase techniques. In last decade, a thorough search is still going on to find more CSPs. For chiral SFC and HPLC, mostly the columns are almost similar and can be selected genuinely. The critical physical column chemistries of the regenerated immobilized cellulose-based materials are summarized in Table 1 [12].

5 Polysaccharides and Polymers of Synthetic Origin

In this learning, cellulose triacetate was established with a varied enantiorecognition capacity via the esterification method using acetic acid (CH_3COOH) and –OH groups of cellulose skeletal structure. One more study was accomplished by Okamoto et al. on CSPs to use cellulose esters as selectors [15]. In this study, they settled that the carbamate and benzoate esters presented the best execution. Table 1 describes several polysaccharide-based fixed phases in the present economic period. Meanwhile, solvent compatibility as a most important issue was founded and wants to be encapsulation by silica like border work. Thus, immobilized CSPs have been bonded covalently through chiral selectors on the silica surface [16–18].

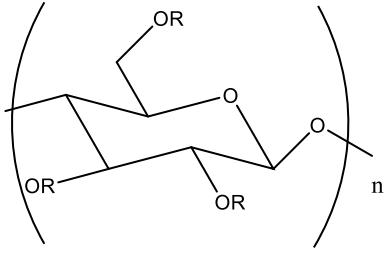
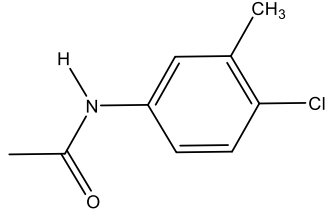
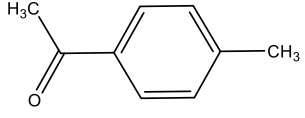
The summary of electron-withdrawing groups like halogens, or electron-giving substituent, like alkyl groups in the structure upgrades the enantioselective bindings. In view of above information, chloro (–Cl) and methyl ($–CH_3$) groups containing polysaccharides have been technologically advanced and observed best performance to be chiral selectors by Chankvetadze and his team [19–21].

Table 1 List of available cellulose-based CSPs

S. no.	Cellulose-based chiral selector	Chemical name of chiral selectors	Local/Brand name	Manufactured by
				
1	R= 	Cellulose tris(3,5-dimethylphenylcarbamate)	Chiralcel-OD/Chiralpak-IB Lux Cellulose-1 Cellucoat Astec Cellulose DMP RegisCell	Chiral Technologies; Daicel Chiral Technologies; Phenomenex; Kromasil; Sigma-Aldrich; Regis Technologies
2	R= 	Cellulose tris(3-chloro-4-methylphenylcarbamate)	Chiralcel OZ Lux Cellulose-2	Chiral Technologies; Phenomenex

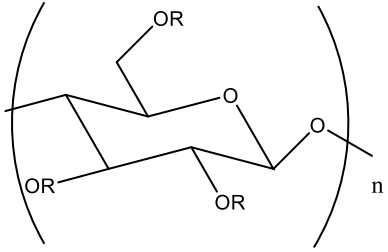
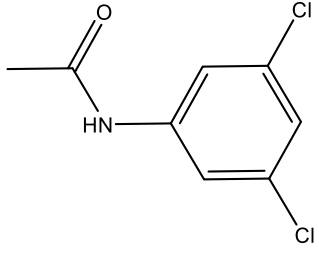
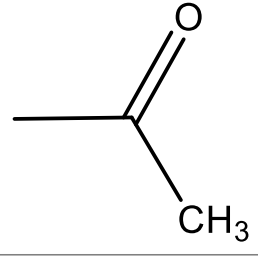
(continued)

Table 1 (continued)

S. no.	Cellulose-based chiral selector	Chemical name of chiral selectors	Local/Brand name	Manufactured by
				
3	R= 	Cellulose tris(4-chloro-3-methylphenylcarbamate)	Lux Cellulose-4	Phenomenex
4	R= 	Cellulose tris(4-methylbenzoate)	Chiralcel OJ Lux Cellulose-3	Chiral Technologies; Phenomenex

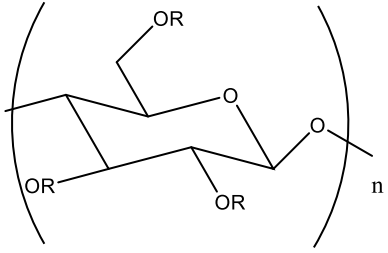
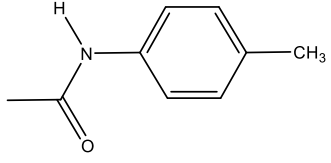
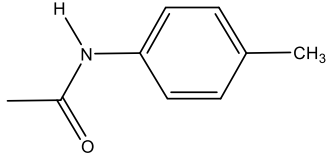
(continued)

Table 1 (continued)

S. no.	Cellulose-based chiral selector	Chemical name of chiral selectors	Local/Brand name	Manufactured by
				
5	R= 	Cellulose tris(3,5-dichlorophenylcarbamate)	Sepapak-5 Chiralpak IC	(Sepaserve) Phenomenex; Daicel Chiral Technologies
6	R= 	Cellulose triacetate	Chiralcel OA	Chiral Technologies

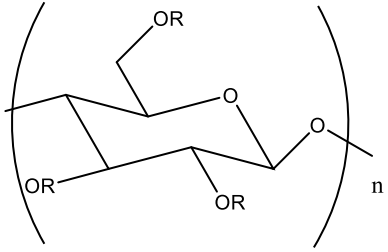
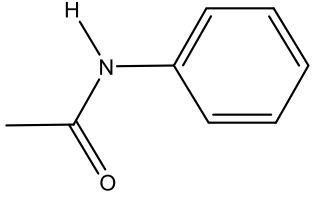
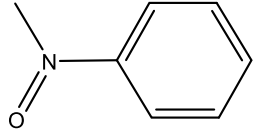
(continued)

Table 1 (continued)

S. no.	Cellulose-based chiral selector	Chemical name of chiral selectors	Local/Brand name	Manufactured by
				
7	R= 	Cellulose tris(4-methylphenylcarbamte)	Chiralcel OG	
8	R= 	Cellulose tris(4-chlorophenylcarbamate)	Chiralcel OF	

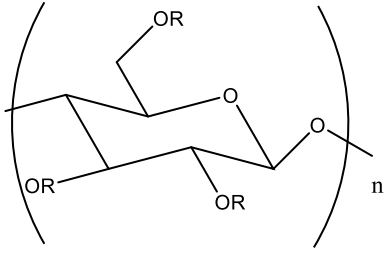
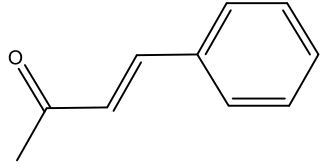
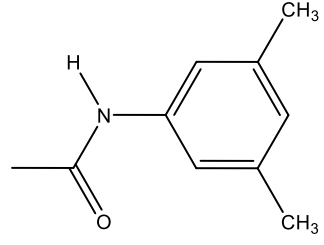
(continued)

Table 1 (continued)

S. no.	Cellulose-based chiral selector	Chemical name of chiral selectors	Local/Brand name	Manufactured by
				
9	R= 	Cellulose tris(phenylcarbamate)	Chiralcel OC	
10	R= 	Cellulose tribenzoate	Chiralcel OB	

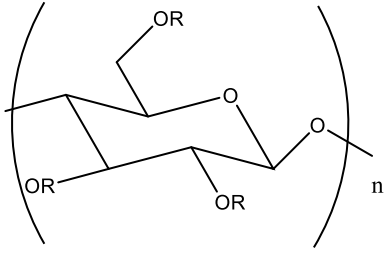
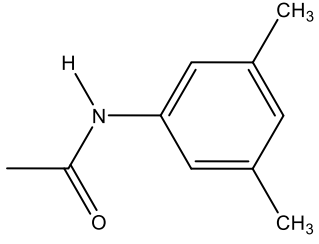
(continued)

Table 1 (continued)

S. no.	Cellulose-based chiral selector	Chemical name of chiral selectors	Local/Brand name	Manufactured by
				
11	R= 	Cellulose tricinnamate	Chiralcel OK	
12	R= 	Cellulose-tris(3,5-dimethylphenylcarbamate)	Chiralpak IBN-5	Daicel Chiral Technologies

(continued)

Table 1 (continued)

S. no.	Cellulose-based chiral selector	Chemical name of chiral selectors	Local/Brand name	Manufactured by
				
13	R= 	Cellulose-tris(3,5-dimethylphenylcarbamate)	Chiralpak IBN-3	Daicel Chiral Technologies

6 Chiral Chromatographic Separation

The chiral separation takes place as a result of some chemical interaction between the chiral stationary phase with the racemate. These chemical interactions may be π–π, dipole–dipole, hydrogen bondings, steric effects and van der Waals forces that fitted with the (enantiomeric) chiral drugs specifically and stereoselective [22–26]. The enantioseparation can be achieved using amylose (α-1,4-linked D-glucose units) or cellulose (β-1,4-linked D-glucose units)-based column chemistry. Amylose-based columns are helical in nature shown in Fig. 5. Similarly, cellulose-based columns are linear in nature and good fit for enantioseparation. Among both, cellulose-based columns show remarkable outcomes due to linear structure of the stationary phases (chiral selectors) such as mentioned in Fig. 6. A comparative chiral separation of atenolol was carried out on both amylose and cellulosed-based columns. The mobile used was a mixture of CO_2 and methanol containing 0.2% triethyl amine (TEA) 60:40 ratio. By using amylose-based Chiralpak IG column on SFC no enantiomeric separation observed Fig. 7. Similarly, cellulose-based Chiralpak IBN-5 column eluted both the enantiomeric peaks with base lined and good resolution as shown in Fig. 8 [27]. This is because of the linear nature of chiral selectors that binds with the atenolol drug enantioselectively. In the chromatogram, both the enantiomeric peaks of atenolol on Chiralpak IBN-5 (Fig. 8) well eluted in run time of 20 min [28–32]. The comparison of both column performance is given with its mechanism. A layout of schematic representation both amylose and cellulose columns is given herein.

7 Conclusion

A brief description of chromatographic techniques based on cellulose-based materials was carried out. The details of other chromatographic technique and their performance were explained in light of cellulose-based packing that utilized in chiral chromatographic separation. A comparison of amylose and cellulose-based packing materials have also been covered in this chapter. Various types of cellulose-based chiral stationary phases were discussed. Briefly, cellulose-based packing materials were showing remarkable outcomes in the area of enantioseparation of racemates. This chapter may be useful for the chromatographers, scientist, pharmaceuticals R & D people, for normal phase and chiral drug development both as well, globally.

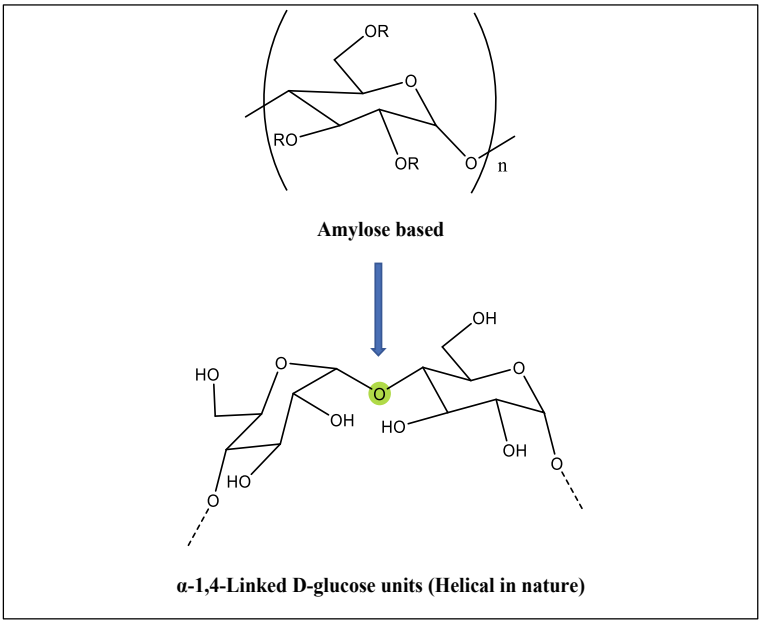


Fig. 5 Chemical structure of α-1,4-linked D-glucose units (amylose based)

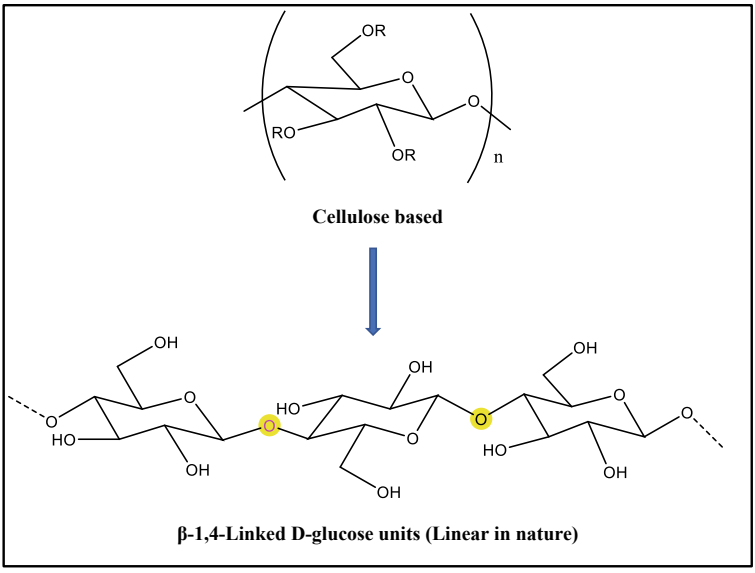


Fig. 6 Chemical structure of β-1,4-linked D-glucose units (cellulose based)

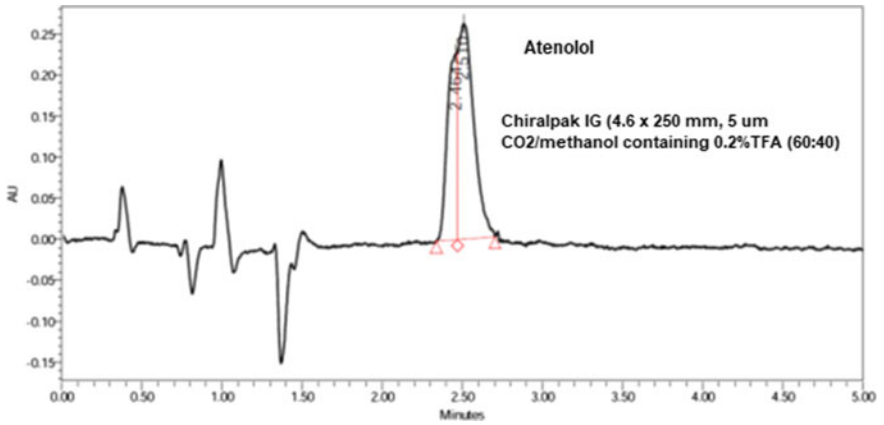


Fig. 7 SFC chiral separation of atenolol using amylose-based (Chiralpak IG) column

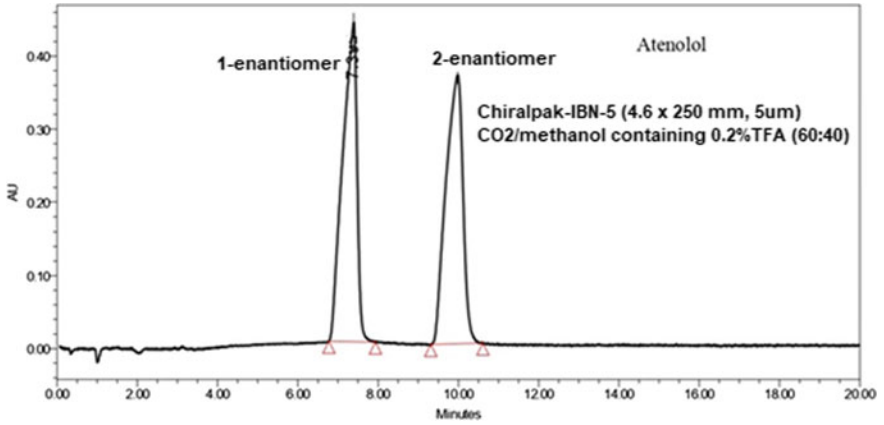


Fig. 8 SFC chiral separation of atenolol using cellulose-based (Chiralpak IBN5) column [27]

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Cellulose Morphologies for Energy Applications

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Abstract Cellulosic materials generated from lignocellulosic biomass are significantly being used for so many applications including for energy application. The exemplary applications range from many types of nanomaterials, bioenergy, conducting materials, battery or electrodes, and also hybrid nanocomposites. The cellulosic materials being generated and reformed for these applications are characterized via its morphological analysis depicting the crucial indicators of benefits and advantages from various lignocellulosic biomass. Common and emerging techniques are discussed on the morphological change on the cellulose before and after formation. The analytical skills required to justify the effectiveness of these applications are presented.

1 Introduction to Cellulose and Energy Applications

Cellulose is a versatile and the most abundant natural polymer on the earth having numerous applications in the field of energy devices, such as supercapacitors, batteries, and solar cells [2, 72]. Generally, cellulose is an insulating material however, it can be converted into an electronically conducting composite material using various types of other conducting polymers to make it a promising candidate for energy storage devices (ESDs) [73, 85]. It is a flexible, sustainable, and a lightweight material that can be extracted from plants, agricultural biomass and paper waste with controllable porosities and pore-size distributions [14, 56, 86]. It has many applications in ESDs (lithium–metal and lithium–sulfur and sodium ion batteries) such

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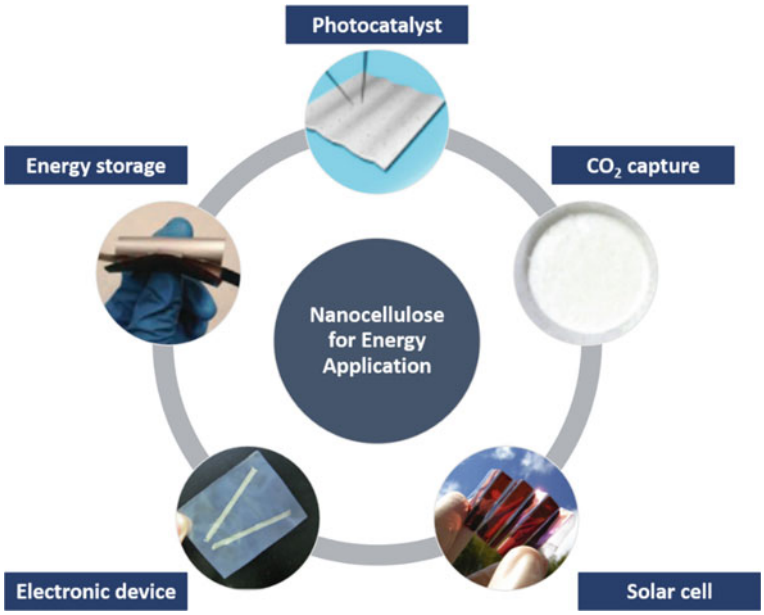

Fig. 1 Application of nanocellulose in energy materials and devices

as inexpensive electrodes, separators, current collectors and electrolytes, exhibiting both high energy and power densities [47, 72, 85].

From Fig. 1, nanocellulose materials can be developed into the high-performance substrate of energy storage devices, solar cells, photocatalyst, and CO_2 capture aerogel.

In the following topics current advances related to cellulose-based conducting materials, their morphologies and respective examples in each energy application will be briefly discussed.

2 Cellulose-Based Nanomaterials in Energy Applications and Morphology

Nanocellulose has been chemically and physically modified to form the flexible substrate for electrochemical energy storage devices, aiming to minimize the ecological footprint. Porous nanofiber offers a high surface-to-volume ratio, which allows a large number of conductive particles to be physically entrapped, contributing to the large energy storage capacity and high-power delivery in a small electrode unit [82]. It can be compounded effectively via film coating, in situ polymerization, and blending strategy with conductive materials of polymers, carbon materials, and metallic particles to form nanocellulose-based composites [13]. These

nanocomposites can serve as alternatives to conventional synthetic materials. They can be supercapacitors (SCs) for higher energy/power density, rate capability as well as long term cyclability [31]. Much interest and studies have concentrated on the development of the advanced nanocellulose-based composite by improving the electrochemical performance using various fabrication. For such, [19] developed nanocellulose-based polyaniline (PANI)/reduced graphene oxide (RGO) composite film electrodes via filtration driven by a vacuum and assembled into sandwich structures for high-performance supercapacitors. A fiber size of nanocellulose film is around 50–100 nm as shown in Fig. 2a. SEM image in Fig. 2b confirms that nanocellulose-based PANI/RGO composite film electrodes have been successfully fabricated. The RGO layers are deposited on the well-grown interconnected PANI and connected with nanocellulose fibers. Small size supercapacitors incorporating nanocellulose substrate also displayed high specific capacitance, conductivity, and flexibility. Figure 2c verifies the flexibility of the composite electrode film using the cyclic voltammetry tests. The assembled supercapacitors as a flat sample and a sample bent at different angles show no significant differences in the cyclic voltammetry curves, indicating the high degree of flexibility of composite electrode films developed for supercapacitors. Therefore, nanocellulose is a highly promising material for advanced energy storage applications due to its excellent electrochemical properties and mechanical properties.

Nanocellulose has been fabricated as ultrathin photovoltaics components for solar cells production. Superior optical properties of the nanopaper can be successfully deposited with conductive materials comprised of indium tin oxide (ITO), carbon nanotubes, and silver nanowire [20]. The fabrication of lightweight and highly portable paper solar cells can supply electric power everywhere by maintaining their high conductivity even after folding [49]. This may result from the high affinity and entanglement between nanocellulose and conductive materials that can still generate electrical energy after repeated folding. The transparent conductive nanopaper also exhibits excellent optical transparency and electrical conductivity as those of ITO glass commonly employed in solar cells. Accordingly, the utilization of conductive nanopaper may achieve a power conversion of 16.17%, which was as high as ITO-based solar cells [79]. The conductive nanopaper was prepared mainly using a nanocellulose substrate of cellulose nanocrystal (CNC) and cellulose nanofibers (CNF) films as bacterial nanocellulose (BNC) films is not transparent due to high light scattering at the nanofibers-air interface [50]. However, both substrates of CNC and CNF also may result in different power conversion efficiency. Costa et al. [10] analyzed solar cells assembled on CNC displayed higher performance than those assembled on CNF. Based on the film morphology of both substrate in Fig. 3, the paper developed from CNC films were smoother with the distribution of fibers being more homogenous and roughness being low. Figure 3c shows the higher transparency of CNC films after the evaporation process. Consequently, a higher photon adsorption rate may be developed from CNC films. This shows the selection of nanocellulose substrate is crucial for producing high-power conversion efficiency of conductive nanopaper in the solar cell.

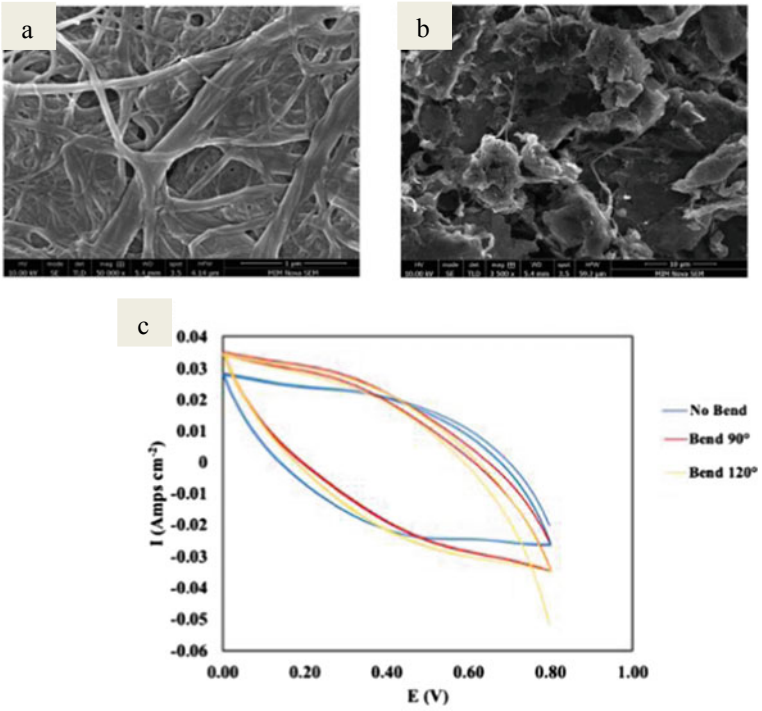

Fig. 2 SEM images of the nanocellulose film and nanocellulose-based PANI/RGO composites, **a** nanocellulose, **b** nanocellulose/PANI/RGO and, cyclic voltammetry curves on the assembled supercapacitor with NC/PANI/RGO electrode film bent at 90°, 120°, and no bending, **c**. *Republished with permission from* [19]

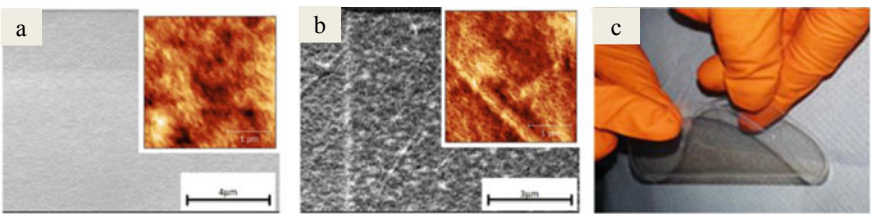

Fig. 3 SEM images of **a** CNC film **b** CNF film and, nanocellulose CNC film **c**. *Republished with permission from* [10]

Besides, nanocellulose material has been extensively explored for photocatalyst application. Nanoparticles for catalysis include precious metals and metal oxide photocatalysts. The nanocomposite of metal nanoparticles such as gold (Au), silver (Ag), platinum (Pt), and palladium (Pd) with nanocellulose are fabricated mainly through metal salts reduction [52]. Nanocellulose is favorable support for metal nanoparticles due to its high surface area, reductive surface functional groups, and

water suspendability. In addition, conventional metal oxide photocatalysts such as zinc oxide (ZnO) and titanium dioxide (TiO_2) were also implemented to nanocellulose structure to enhance the photocatalytic activity [64]. Researchers have employed cellulose-based metal oxide nanostructures as thin films, membranes, fibers, and hybrids for the photocatalytic treatment of wastewater under UV and visible light. Thus, the nanocellulose composite can be applied to the treatment of polluted water by decomposing organically-based pollutants through catalytic activity. Generally, nanocellulose catalysts prevent nanoparticles from aggregating. Wei et al. [77] observed the morphology of ZnO photocatalyst. The synthesis of ZnO prepared without nanocellulose can be characterized as flakes with 1 μm length. According to Fig. 4a, these micro flakes were randomly aggregated together. However, the presence of nanocellulose may reduce the ZnO coacervate as well-dispersed flakes can be observed in Fig. 4b. Excellent photocatalytic performance also was evaluated from ZnO/nanocellulose composite as depicted in Fig. 4c. Comparatively, the ZnO/nanocellulose composite achieved a faster degradation rate within 30 min than ZnO prepared with different additives such as TiO_2 P25 catalyst, microcrystalline cellulose (MCC), and glucose. Thus, the newly synthesized nanostructure cellulose-based is anticipated to be a promising photocatalyst.

Nanocellulose is also ideal building blocks to construct lightweight porous materials, such as aerogels. The nanocellulose aerogels were utilized as CO_2 selective adsorbents or constituents of membranes. Physical crosslinking through hydrogen bonding or chemical cross-linked hydrogel may transform nanocellulose to aerogels by freeze-drying cycles [43]. However, nanocellulose aerogel is less selective toward CO_2 without chemical modification. Thus, modification of nanocellulose with silanes such as *N*-(2-aminoethyl)-3-aminopropylmethyldimethoxysilane (APMDS) was used to enhance the CO_2 adsorption capacity [38]. The APMDS-CNC aerogel in Fig. 5b is characterized by a honeycomb structure, with squares, polygons, and circles very much more visible than the CNC aerogel that is unmodified in Fig. 5a. Based on the solid-state NMR analysis in Fig. 5c, nanocellulose was successfully modified with APMDS. The result shows the six characteristic signals of cellulose in the 60–120 ppm range were detected in the AEAPMDS-CNC NMR spectrum. As compared to the bare CNC, no shifting of these signals was observed, although

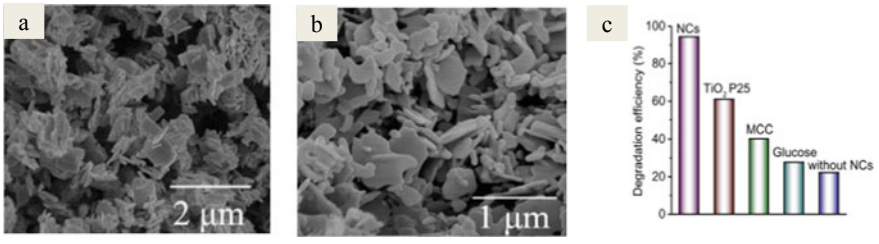

Fig. 4 SEM images of ZnO prepared **a** without nanocellulose, **b** with nanocellulose and, ZnO degradation efficiency **c**. *Republished with permission from* [77]

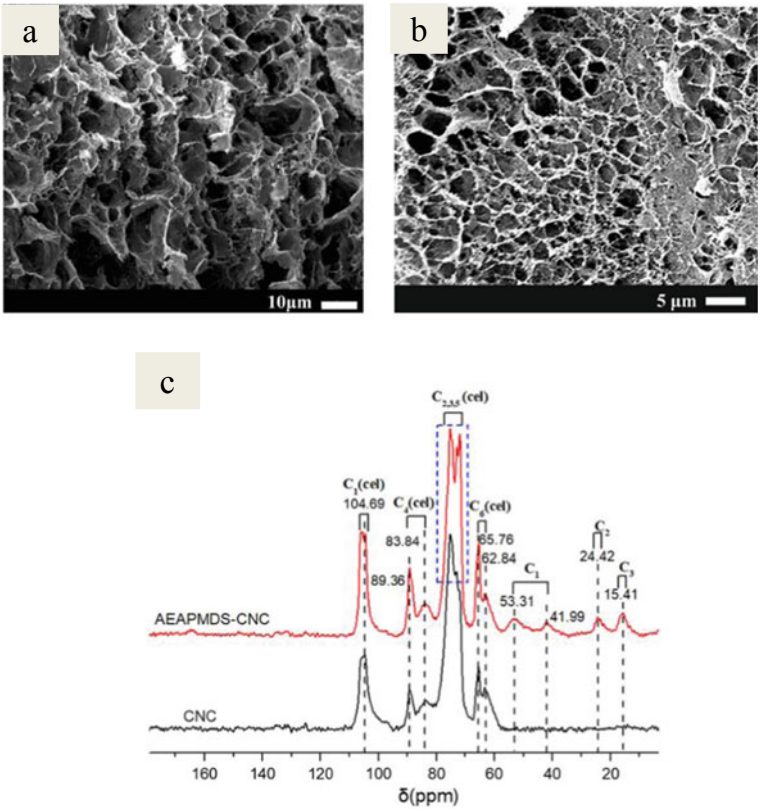

Fig. 5 SEM images of **a** CNC aerogel **b** APMDS-CNC aerogel and ^{13}C CP/MAS NMR spectrum o of CNC and APMDS-CNC aerogel **c**. *Republished with permission from* [71]

the intensity of C2/C3/C5 and C6 signals increased. The findings proved the chemical structure of cellulose was maintained, indicating the successful grafting of the AEAPMDS into CNC. The grafting process of APMDS onto CNC also resulted in a low shrinkage rate and a high specific area for a higher adsorption rate of CO_2 [71]. Hence, the aerogels of nanocellulose pre-functionalized by APMDS were preferable as green adsorbent material for rapid and effective removal of CO_2 from the atmosphere.

Another energy application of nanocellulose includes the development of transparent nanocellulose paper for electronics devices. Generally, electronic devices are replaced regularly and discarded after a short lifespan. In turn, this poses a growing environmental threat because of the widely used materials, comprised of plastics, glass, and silicones, which are both non-biodegradable and non-recyclable. Therefore, transparent nanocellulose paper was developed and used in electronic devices such as transistors, organic light-emitting diodes, antennae, and touch sensors. For

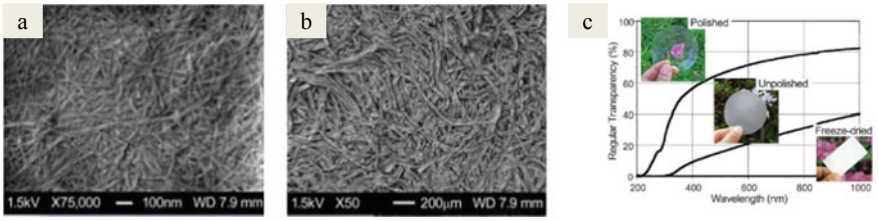

Fig. 6 SEM images of **a** cellulose nanofiber paper **b** raw paper and, light transmittance of the cellulose nanofiber sheets. **c**. *Republished with permission from* [50]

instance, [24] prepared a highly transparent organic transistor device using nanocellulose paper as the substrate. Nanopaper transistors exhibit superior electrical properties, with carrier mobility of around 4.3×10^{-3} $cm^2/(Vs)$. A simple vacuum filtration method followed by oven drying, pressing or freeze-drying can be used to prepare nanocellulose paper [63]. In contrast, nanopaper exhibits higher transparency than raw paper that may enhances photon absorption [72]. According to [11], a nanopaper possesses an optical transmittance of 90%, whereas raw paper has an optical transmittance of 20%. The different levels of transparency may be explained by the width of the fiber and the size of the cavities, as shown in Fig. 6a. Optically transparent nanofiber paper in Fig. 6a is composed of 15 nm cellulose nanofibers. Meanwhile, the raw paper depicted in Fig. 6b is composed of 30 mm pulp fibers. In the fabrication of cellulose nanofiber paper, the sheet was freeze-dried and mechanically compressed at 160 MPa under a vacuum to remove air and voids. The obtained dried sheet wasn't optically transparent as shown in Fig. 6c. Therefore, the sheet was polished with emery paper (4000 and 15,000 grit) to improve transparency. The polished cellulose nanofiber sheets achieved 71.6% light transmittance and surface reflection at a wavelength of 600 nm. The sheet also can be folded, despite its plastic-like transparency. This study paves the way for the development of nanopaper for flexible electronics devices.

3 Cellulose Conversion to Green Bioenergy and Morphology

The conversion of cellulosic materials to bioenergy is a rapidly developing strategy that is widely examined. Similar to fossil fuels, bioenergy can be further classified into three forms which are solid, liquid, and gas. Bioenergy is a renewable energy that has potential to be directly used or converted to transportation fuels, heat, electricity, and many other bioproducts. Solid bioenergy are commonly found in the forms of firewood, woodchips, wood pellets, and charcoal; liquid bioenergy in the forms of bioethanol and bio-oils; and gas bioenergy in the forms of hydrogen, biogas, and

syngas [16, 27]. These bioenergies are derivable from cellulosic materials via either thermochemical or biochemical conversions as illustrated in Fig. 7.

Each of these bioenergy plays its own specific role in contributing to the future development of green energy. Interestingly, the energy contents of bioenergies are comparable with those of fossil-based fuels. Table 1 lists the energy contents of fossil fuels and bio-based fuels. To further explain, the energy contents of solid bioenergies are almost similar to half the energy contents of gasoline and diesel. Meanwhile, the energy contents of liquid bioenergies are in close proximity with those of fossil fuels, which makes it possible to be blended together. On the other hand, gaseous bioenergies reported higher energy contents compared to fossil fuels. These values exhibit the potential of bioenergies in possibly replacing fossil-based fuels in the near future.

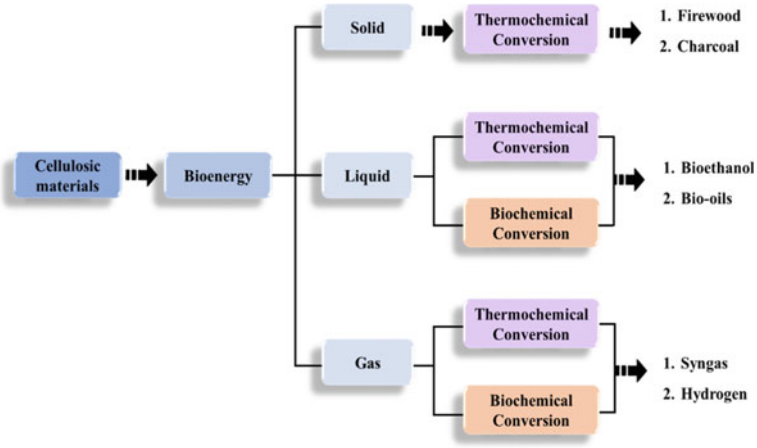

Fig. 7 Conversions of cellulosic materials to bioenergy

Table 1 Energy contents of fossil fuels and bioenergy

Fuel type		Energy content (MJ/kg)	References
Fossil fuel	Gasoline	48.5	[18]
	Diesel	45	[18]
Solid bioenergy	Firewood	15–17	[41]
	Charcoal	28–29	[41]
Liquid bioenergy	Methanol	20–23	[26]
	Ethanol	27–30	[26]
	Butanol	33–36	[26]
Gas bioenergy	Methane	50	[55]
	Hydrogen	120	[55]

Initially, firewood was the primary source of fuel for domestic utilization prior to the discovery of fossil fuels [15]. Firewood can be used to produce bioenergy in the forms of heat and fuel through pyrolysis process. Accordingly, firewood is combusted at high-temperature ranges of 220–300 °C through exothermic pyrolysis to form char and gaseous fume which then ignites to flame. On the other hand, charcoal is another form of solid bioenergy that is obtainable from cellulosic materials. It is a carbon-enriched, porous, and grayish black solid that is produced from the pyrolysis of wood at temperature range of 600–1100 °C, under oxygen limiting environment [27]. As the temperature rises in the range of 240–310 °C, the carbon–oxygen and carbon–carbon bonds in the cellulose structure begin to be disrupted which escalates the formation of charcoal. As the temperature rises, cellulose structures begin to completely disrupt to form charcoal as the final product. This phenomenon had been observed by [35], where the crystalline structure of wood detected under X-ray diffraction (XRD) disappeared once the temperature reaches above 350 °C, as shown in Fig. 8. Charcoal is an already existing solid bioenergy that is commonly used for purposes such as cooking, barbeque, and steel making.

Currently, great interest had been shown in the production of hydrogen (H_2) fuel, which is a biogas that is producible from cellulosic materials conversion. H_2 has an extensive contribution to the fuel sector and it is one of the main gas that is utilized in majority of the refinery operations [36]. In addition, H_2 can be used in fuel cells to generate electricity [3, 36]. Attractively, H_2 only yields water (H_2O) as the end product of combustion which makes it a clean fuel. H_2 can be converted to liquid fuels through Fischer–Tropsch synthesis, and it has capability to be used

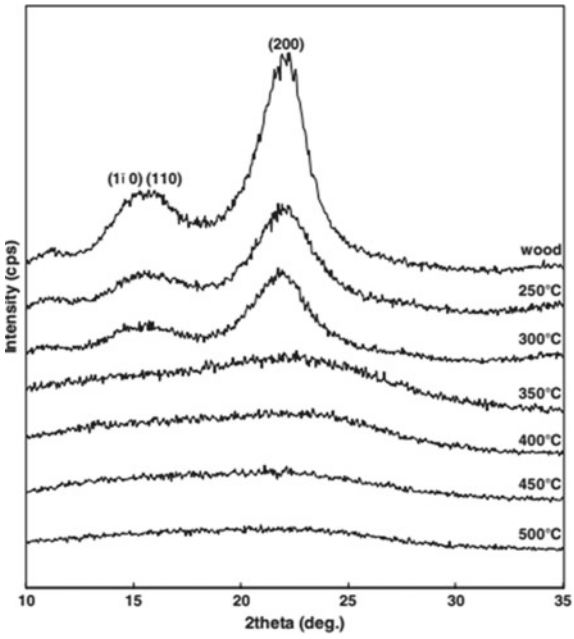

Fig. 8 XRD of wood at different carbonization temperatures. *Republished with permission from* [35]

in internal combustion engines [3, 16]. This fuel has grabbed the interest of many due to its advantageous characteristics of having high octane number, no toxicity, broader flammability limits and rapid burning speed [36]. The production of H_2 from cellulosic materials can be achieved via thermochemical and biological conversions, owing to their own pros and cons. Thermochemical conversion of cellulosic materials begins with the production of syngas, from which H_2 is then separated and purified as illustrated in Fig. 9. Syngas is a mixture of carbon monoxide (CO), carbon dioxide (CO_2), methane (CH_4), and hydrogen (H_2) gaseous which is produced through gasification reaction conducted at temperature range of 600–1000 °C [4, 6, 66]. The obtained syngas is then subjected to water gas shift reaction and pressure swing adsorption. Water–gas shift reaction helps in the conversion of CO to H_2 and CO_2 under the presence of water, and pressure swing adsorption is then used to capture the produced CO_2 to yield a high purity of H_2 gas [36]. A reported study by [60], successfully synthesized 6.52, 4.26, and 4.1 mmol of H_2 from 1 g of wheat straw, walnut shell, and almond shell, respectively, via gasification process in supercritical water media.

Although thermochemical conversion of cellulosic materials is a fast process, char and tar are often formed during the decomposition of cellulosic materials and it is also a highly energy-intensive process. That being mentioned, biological conversion of cellulosic materials to H_2 is a less energy-consuming and eco-friendly process. Photofermentation and dark-fermentation are the two types of biological conversions that can be conducted on cellulosic materials to yield H_2. These fermentation processes can either be conducted individually in a single-stage reaction or combined together as a dual-stage reaction as depicted in Fig. 10. In the dark-fermentation method, anaerobic microorganisms are used to ferment the cellulosic materials under low

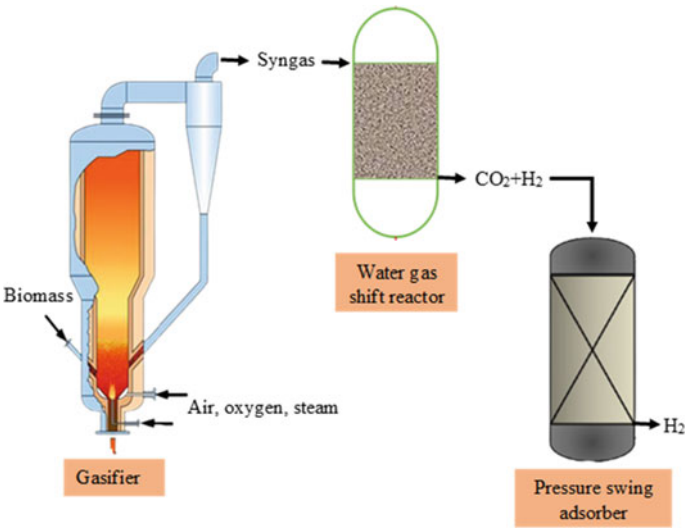

Fig. 9 Thermochemical conversion process of biomass to hydrogen

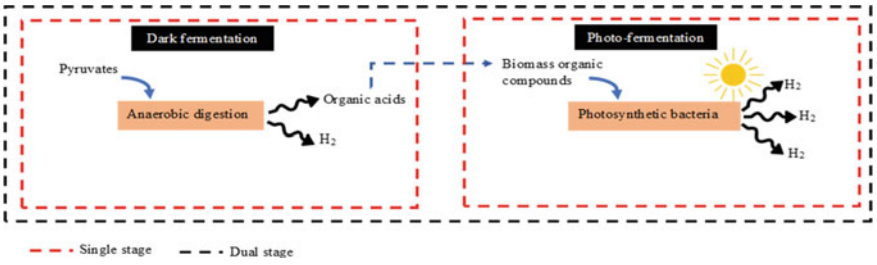

Fig. 10 Single-stage and dual-stage biological conversion of cellulosic materials to hydrogen

temperatures [61, 83]. Briefly, during this fermentation, the anaerobic metabolysis of pyruvates obtained from glycosis takes place to produce H_2 along with CO_2 [83]. It has been reported that for per mol of glucose, 4 mol of H_2 can be produced with acetic acid as the by-product, and 2 mol of H_2 can be produced with butyric acid as the by-product [3, 81]. For instance, [42], had achieved direct H_2 production from cellulosic materials via dark-fermentation process. In this study, 1.27, 1.18, and 1.24 mmol of H_2/glucose were obtained from dark fermentation of dried distiller grains, contaminated barley hulls, and barley hulls using *Clostridium thermocellum* bacteria. On the contrary, photo-fermentation method involves the conversion of organic compounds derived from cellulosic materials to H_2 using photosynthetic bacteria such as purple non-sulfur bacteria with the aid of solar energy [36, 61]. Notably, photo-fermentation is a light dependent process whereas dark fermentation is a light independent process. In recent advances, the dual-stage combination of both fermentative methods are being studied to yield higher H_2 productions [61]. In this combination method, cellulosic materials are converted to H_2 and acetic acid via dark-fermentation method in the first stage, followed by the second stage where the produced acetic acid is converted to H_2 via photo-fermentative method yielding higher amounts of H_2 compared to the individual biological conversion.

Liquid bioenergy in the forms of bioethanol and bio-oils are extensively studied due to their extraordinary potential to substitute commercial liquid fuels. Bioethanol is a biofuel that can be obtained from cellulosic materials via biochemical and thermochemical conversions [27, 69]. The biochemical conversion of cellulosic materials to bioethanol involves either separate hydrolysis and fermentation (SHF) process or simultaneous saccharification and fermentation process (SSF) [39, 67]. Figure 11 illustrates the SSF and SHF conversions of lignocellulose to bioethanol. In SHF process, cellulosic materials are first subjected to hydrolysis to convert the long-chain polymeric cellulose to readily digestible monomeric sugar such as glucose. There are two types of hydrolysis, namely acid hydrolysis and enzymatic hydrolysis where the latter has advantages of being environmentally friendly. Post hydrolysis, the monomeric sugar glucose is fermented under anaerobic conditions in the presence of microorganisms to produce bioethanol and water [16, 69]. Meanwhile, in SSF, both saccharification and fermentation of cellulosic materials occur simultaneously in one single fermenter to produce bioethanol and water [16]. In most cases, SSF is

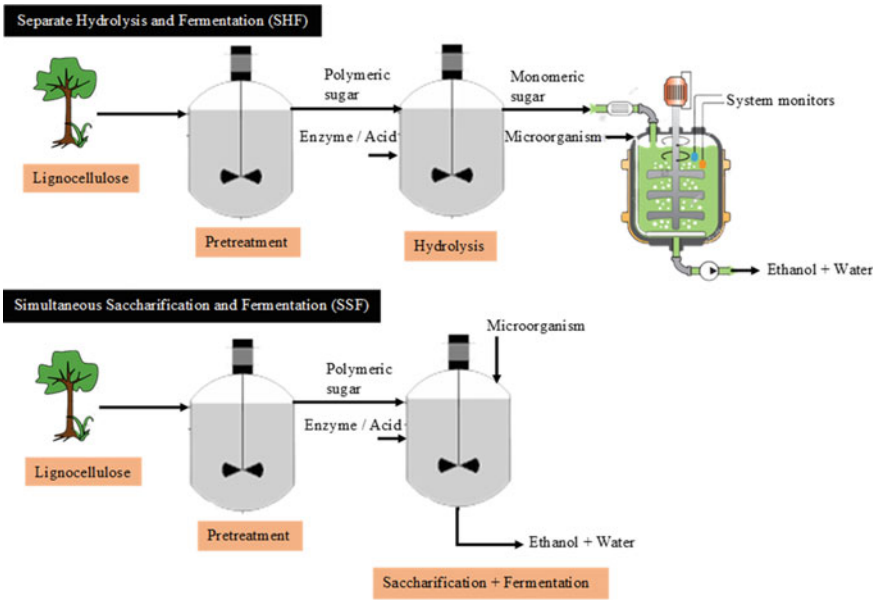

Fig. 11 SHF and SSF conversions of polymeric sugars to ethanol

preferred over SHF cause through SSF, the concentrations of saccharides formed are kept low and it is more cost-effective [39].

The thermochemical conversion to produce bioethanol begins with the conversion of cellulosic materials to syngas first, which is conducted via gasification at high temperature. The produced syngas is then converted to bioethanol via catalyzed fermentation under the presence of microorganisms. During the fermentation process, the microorganisms consume the syngas for energy and subsequently generate ethanol and water [15, 39]. Noteworthy, the product of both thermochemical and biochemical conversions are a mixture of bioethanol and water. Thus, post-conversions the product mixture undergoes fractional distillation to separate and purify the bioethanol from water [39]. Fractional distillation works on the basis of component boiling points. Bioethanol has a lower boiling point compared to that of water, and thus bioethanol evaporates first and is collected as distillate. It has been reported that the bioethanol yield can be obtained up to 50% of the syngas mass [15]. Table 2 lists the fuel properties of gasoline and ethanol. Uniquely, bioethanol has broader flammability limits, higher octane number, higher heat of vaporization, and higher flame speeds that subsequently increase the thermal efficiency of fuels, which makes it a promising candidate to replace gasoline [69]. Interestingly, bioethanol can be blended up to 10% with gasoline to be used in petrol engines which promotes cleaner burning fuels and also reduces the dependency on fossil fuels [15].

Table 2 Comparison between fuel properties of gasoline and ethanol. *Republished with permission from* [58]

Fuel property	Gasoline	Ethanol
Composition (C, H, and O) (wt%)	86, 14, 0	52, 13, 35
Flammability limit (vol%)	0.6–8	3.5–15
Octane number	90	106
Heat of evaporation (kJ/kg)	380–500	904
Flame speed (m/s at 25°C)	0.33	0.41
Density (kg/m^3)	0.742	0.79

Bio-oils are another type of liquid bioenergy that can be produced from cellulosic materials and biobutanol is one of the examples of extensively studied bio-oil. Bio-oils are commonly produced by subjecting cellulosic materials to fast-pyrolysis at very high temperatures [28, 40]. It has been reported that the bio-oils can yield up to 80% of dry feed [4, 25]. These bio-oils are dark in color and contain a mixture of water with oxygenated organic compounds such as aldehydes, ketones, phenols, esters, alcohols, and furans [16, 28]. Bio-oils can be utilized as substitutes to fuels and diesels in boilers, furnaces, engines, and turbines for generation of heat and power [4]. Moreover, bio-oils can also act as precursors for the synthetization of transportation fuels. Furthermore, bio-oils can also act as fuel additives where they can be directly "dropped-in" commercial fuels that help in improving the engine compatibility issues [40].

4 Cellulose-Based Conducting Materials, Battery or Electrodes Applications and Morphology

4.1 Cellulose-Based Conducting Materials

As cellulose is an insulator so, electronically conducting components such as carbon nanotubes (CNTs), carbon fibers, graphene, conducting polymers, transition metal oxides, and intercalation compounds clearly need to be included for its applications in ESDs [47, 51, 73]. The hydroxyl groups present on the cellulose surface allow strong interactions with the electroactive active components such as conducting polymers (polyaniline, polypyrrol) and other conducting agents (CNTs, carbon fibers and graphene) [44, 75, 86].

Generic approaches for making conductive NC-based materials have been summarized in Fig. 12. Although there are number of available conducting materials that can be used however, practically the cost, the level of the conductivity, chemical and physical stabilities, biodegradability, toxicity, environmental concern and ease of preparation need to be considered [13]. In recent years, the research efforts have been devoted to fabricate conductive nanocomposites by combining conductive polymer (especially PPy and PANI) with NCs [7]. Two major approaches are usually employed

to fabricate NCs-based conductive hybrids which include: coating the conductive materials on the surface of cellulosic substrate and mixing of conductive materials inside of NCs substrate to make a composite. In the first method various types of surface coatings on the surface of NC can be applied, such as particle, solution, vapor deposition, sputter coating. For the other strategy, in situ polymerization and blending are mainly involved in fabrication of the composite [13]. In these four methods, the in situ polymerization is a common way to introduce conductive polymer into a NCs matrix. The well-dispersed NCs are impregnated with a monomer and then an encapsulated NCs/polymer nanocomposite is produced by the addition of an initiator [80]. In blending, conductive hybrid materials also combines the strength of individual added materials like metallic particles or carbon allotropes. Mixing of PANI with cellulose acetate (CA) either by casting of films from a suspension of PANI in a CA solution or putting CA films onto electrochemically prepared PANI as CA films does not obviate the redox process of PANI [54].

Encapsulating process was used by [30] to prepare conducting composites from Kraft paper pulp with PPy and PANI via direct polymerization of the respective monomers using ferric chloride and ammonium persulfate as the oxidants. The composites exhibited the electrical and chemical properties of the conducting polymers and the strength, flexibility, and available surface areas of the cellulose fiber. Because carbon materials have higher conductivity than conductive polymer, therefore, relatively high conductive NC sheets can be made from carbon-CN composites. Most of conductive carbons/NCs composites feature the use of carbon nanotubes (CNTs) or graphene, two relatively new materials with astounding properties [13]. It was also observed that the porous structure of cellulose leads to more conformal coating of the conductive materials because of its strong capillary force and large contacting surface area.

In addition, via a simple carbonization process, cellulosic materials can be transformed into electronically conductive carbon materials with high specific surface areas and rich pore structures. These characteristics make cellulosic materials suitable for use as flexible/transparent substrates, separators, electronic–ionic conductors, electrolytes, and electrochemical electrode materials in flexible circuits or sensors, conductive transistors, organic light-emitting diodes (OLEDs), organic thin-film transistors (OTFTs), supercapacitors, batteries, triboelectric nanogenerators (TENGs), tissue bioelectronics, and other flexible electronics [86]. So, in spite of being inherently non-conductive, cellulose fibers are widely known for their mechanical strength and flexibility, which makes them suitable substrates for reinforcing conductive polymers to significantly enhance their electrochemical properties (Fig. 12).

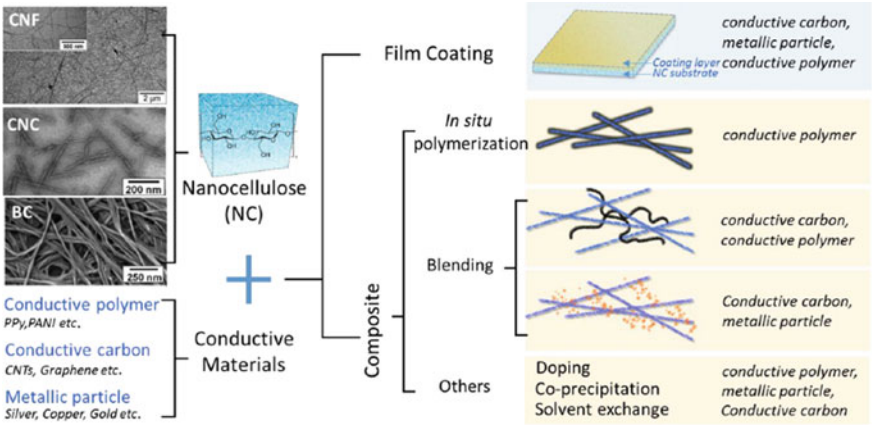

Fig. 12 Schematic illustration of the generalized fabrication routes to nanocellulose (NC) based conductive hybrid. *Republished with permission from* [13]

4.2 Applications of Cellulose-Based Conductors in Battery Components

4.2.1 Cellulose-Based Battery Electrodes

Based on different properties of various types of cellulose, it is clearly important to carefully select and describe the type of cellulose to be used in the particular component of cellulose-based electrochemical ESDs. Particular attention is paid to the development of cellulose-based electrodes with high energy densities, power densities, and mass loadings. The later requires proper selections of the types of cellulose employed as well as optimized electrode porosities since a too low or a too high porosity will lead to either mass transport limitations (i.e., decreased power densities) or decreased energy densities (due to excessive amounts of electrolyte in the pores of the electrode) [76, 86]. When cellulose is used in electrochemical energy storage devices, the water content of the cellulose is an important factor, particularly for supercapacitors and batteries containing non-aqueous electrolytes. The water problem is naturally also minimized if low amounts (e.g., 10%) of cellulose are used in electrodes [57, 87]. Conventional electrodes and separators are commonly vacuum dried at 80 °C, while a slightly higher drying temperature (e.g., 120 °C) is required for wood- and bacteria-based electrodes, separators, and current collectors.

As cellulose-based electrodes generally are mechanically flexible they are assumed to be able to handle the strain arising within the material during the charge and discharge of the paper electrodes, thereby improving the electrochemical stability of the electrodes [59]. One promising approach to manufacture cellulose-based electrodes involves the immobilization of an electroactive material on the surfaces of the cellulose fibrils using a dispersion of cellulose fibrils, CNTs, or carbon fibers, and the electroactive material in, e.g., water [34, 88]. The immobilization can either result

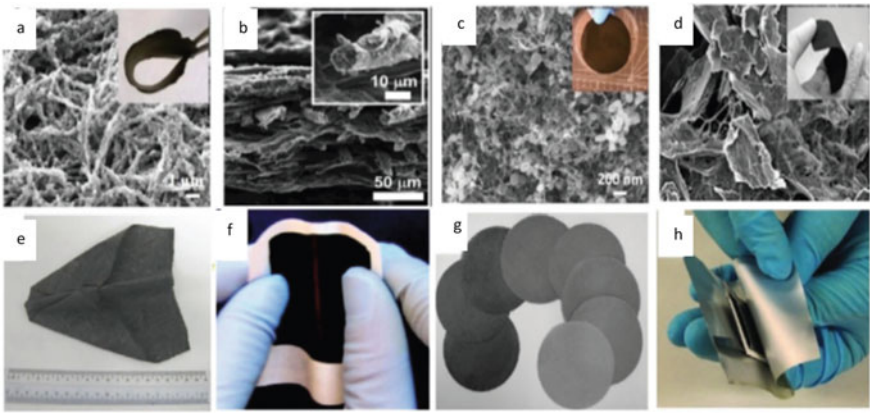

Fig. 13 **a** and **b** SEM images of polypyrrole (PPy)-coated cellulose paper electrodes containing nanocellulose and CMF. **c** SEM image of a flexible silicon paper electrode with silicon nanoparticles embedded in a matrix composed of carbon nanotubes (CNTs) and nanocellulose. **d** SEM image of a nanocellulose-graphite anode composite paper. The inset shows optical photo of composite paper with flexibility. **e** Optical photo of a foldable paper electrode composed of a graphene/polyaniline/cellulose composite. **f** Optical photo of a flexible Li-ion paper battery with a paper separator and integrated CNT/nanocellulose current collectors. **g** Graphite/cellulose composite papers with decreasing cellulose microfiber content from left to right. **h** A paper-based electrochemical energy storage device composed of two Ppy/nanocellulose paper electrodes, a cellulose separator and graphite current collectors. *Republished with permission from* [73]

from adsorption of the electroactive components on the cellulose fibrils and CNTs, or the formation of a coating as a result of a chemical reaction. Various types of electrodes prepared using different conductive cellulosic materials have been shown in Fig. 13.

To obtain well-functioning electrodes composed of these cellulose/active material composites, it is very important to optimize the electrode porosity and to design efficient conductive network enabling rapid electron/ion diffusion within the electrodes. The hydroxyl groups present on the cellulose surface also allow strong interactions with the electroactive active components and conducting agents (e.g., CNTs or carbon fibers). This facilitates the formation of uniform coatings with porous structures of the nanocellulose-based electrodes [2, 72, 85]. Various conductive materials have been used for the fabrication of electrodes. Carboxymethyl cellulose (CMC)-based electrode materials, along with binder and gel electrolytes, are extensively used to construct supercapacitors, batteries, and electrocatalysts. [53] successfully synthesized CuO/CMC and CuO@MnO_2/CMC composites via a hydrothermal process. Cellulose electrodes were also prepared by in situ synthesis of PANI on regenerated cellulose microspheres (CM) using phytic acid (PA). Due to this homogeneous micro- and nanoporous architecture, the PANI/PA/CM exhibited excellent cycling stability (over 12,000 cycles), high-rate capability, and good conductivity as an electrode material.

The 3D nanostructures obtained from CNFs are already being implemented in electrode design, and might have a strong impact on the future design of energy storage devices [14]. BNC, with its high content of superfine nanofibers (40–60 nm), large specific surface area, and high crystallinity, essentially offers nitrogen-doped carbon networks via coat of PANI and polyamide on BC. Papers are suitable candidates for substrates in flexible energy storage applications due to their natural tendency to integrate with conductive materials, such as carbon nanotubes. In general, BNC fibers smaller (20–100 nm) than those of conventional cellulose fiber (10 mm) are considered suitable for paper electrodes [70]. Flexible electronics contain electrode materials that outperform conventional activated carbon for supercapacitor application. For example, carbon nanotubes (CNTs) ensure high flexibility, while providing long, continuous conductive paths. The fabrication of flexible electrodes from CNF is possible due to its high elastic modulus and low thermal expansion, so that it is capable of hosting a range of guests required for flexible electrodes [34, 75]. Flexible cellulose-based electrode materials generally are used in the form of a composite of nanostructured cellulose and Ppy, constructed by the chemical oxidation of Ppy in the presence of cellulose extracted from green algae [45]. Hu's group reported a conductive nanofiber network for high-loading thick electrodes, in which neutral carbon black nanoparticles were attached to negatively charged CNFs. The obtained conductive nanofiber electrode had a close-packed layer-by-layer structure in which the carbon black particles were entrapped. It displayed good mechanical flexibility and high electrical conductivity based on the decoupled electron/ion transfer pathways [37].

An important application of cellulose in LIBs is the binder in both cathode and anode for electrode materials. Although binders are not the most essential component in LIBs, they can greatly affect the properties of electrodes, particularly their mechanical and electrochemical performance [37, 72]. Current LIB technology uses PVDF as binders and requires the use of volatile and toxic solvents for processing, such as *N*-methyl-pyrrolidone (NMP). Therefore, fluorine-free aqueous binder replacement is desired to address the economic, environmental, and safety concerns, paving the way toward safer and greener LIBs. In this regard, water-soluble carboxymethyl cellulose (CMC), a derivative of linear polymeric cellulose with substitutional anionic carboxymethyl groups in various degrees, is frequently used [5]. The focus of electrode design and development in LIBs is on the enhancement of electrons and lithium-ion conductivity, which can further improve the performance of LIBs [29].

4.2.2 Cellulose-Based Electrolytes

An electrolyte can be defined as a liquid or type of gel which contains specific conductive ions that allows for the ionization or flow of electrical charge between the electrodes. After the use of first polymer electrolyte in 1973, it was found that this polymer electrolyte is a much better alternative to liquid electrolyte due to its excellent mechanical and thermal stability and high ionic conductivity [62]. Now a days solid polymer electrolytes (SPEs) are the key material of all-solid-state energy devices

such as solid-state batteries (SSBs), and have been extensively studied in the fields of materials science, polymer science, and electrochemistry [73, 85, 86]. SSBs play a vital role in the development of science and technology, from portable electronics on one extreme to electric vehicles and backup power sources in aircraft. Using SPEs in SSBs can also solve the problems associated with conventional liquid electrolyte battery systems such as spillage, difficulty in handling liquids during manufacturing, corrosiveness, low power to weight ratio and limited shelf life [5]. Synthetic polymers such as polyethyleneoxide, polyacrylic acid, and polyvinyl alcohols got much attention in the preparation of SPEs but their high cost and the depletion of petroleum resources provide the impetus for search of new natural, economical and environment friendly materials [46]. Cellulose and its derivatives are one of the several renewable resource-based biopolymer materials that have been discovered and used as host polymers and building block in the biopolymer solid-state electrolytes [46, 65, 86]. Samsudin et al. [62] has used carboxymethyl cellulose as a host polymer in his work for developing proton-conducting biopolymer electrolyte while NH_4Br was chosen as the ionic dopant and proton donor. Another problem using conventional electrolyte polymers is the lack of mechanical strength which limits their application in as-prepared LIBs. In order to satisfy both conductivity and mechanical aspects, fillers/nanofillers can be added into the electrolyte system [13, 17]. NC, as a good reinforcing material, has received great attentions. High-performance LIBs can be prepared with NC employed as the nanofiller in the electrolyte polymer matrix, which improves transport properties and the stability of the electrode–electrolyte interface [6, 32].

The high aspect ratio of cellulose, along with its good wettability and thermal stability in various electrolytes, is conducive to a wide potential window, making cellulosic materials attractive as dielectric materials or gel electrolytes for flexible OLEDs, foldable batteries, and printed photovoltaic cells. For energy storage devices containing non-aqueous electrolytes, the water content of the cellulose is another important parameter. In these cases, celluloses with high degrees of crystallinity, e.g., *Cladophora* cellulose, CNCs, and tunicate cellulose, are particularly promising since they can decrease the problem associated with the presence of water in the charge-storage devices [57]. With the additional ability to generate an effective solid-electrolyte interphase layer, cellulose-based polymer electrolytes play an important role in improving the rate capability and reversibility of lithium plating and stripping. Dong et al. designed a BC-supported poly(methyl vinyl ether-*alt*-maleic anhydride) polymer electrolyte for LIBs, which exhibited good mechanical properties [12]. Nair et al. [48] used a natural modified cellulose hand sheet in a methacrylic-based thermos-set gel-polymer electrolyte. The cellulose composite exhibited excellent mechanical properties and preserved the good electrochemical performance. Willgert et al. [78] developed poly(ethylene glycol) (PEG) electrolyte reinforced with CNF paper, which improved the ionic conductivity when the composite was swelled with liquid electrolyte. An ionic conductivity of 5×10^{-5} S cm^{-1} and an elastic modulus around 400 Mpa at 25 °C were obtained. The manufacture of NC-based energy

devices at an industrial scale also strongly depends on the development of production of nanocellulose materials. Availability of low-cost NC materials commercially, will further attract more research attentions of NCs in ESDs and supercapacitors.

4.2.3 Cellulose-Based Separators

One of the most critically important battery components to ensure safety is the separator, a thin and porous membrane that physically separates the two electrodes to prevent short circuit while facilitating ion transport as well as mechanical robustness. In LIBs, a separator material should possess essential properties, such as chemically and electrochemically stability, good wettability to liquid electrolytes, strong mechanical strength, proper thickness, appropriate pore diameter, and porosity along with excellent thermal stability [65]. Polyolefins-based separators such as polyethylene (PE) and polypropylene (PP), are conventionally used in LIBs [1, 13], however, the intrinsically hydrophobic character, low porosity, insufficient electrolyte wettability, weak mechanical, and thermal properties limit their practical application [9]. Generally, the use of pure cellulose-based separators in rechargeable LIBs are hindered due to its hydrophilic nature, poor mechanical properties, degradation tendency with lithium ions. However, due to the highly crystalline nature, regular and precise long rigid rod shape and high aspect ratio, cellulose nanofibers (CNF) are considered as an excellent alternative to improve the material properties of different polymer matrixes either of natural or synthetic origin [54]. The chemical and thermal stability of CNF can meet the key requirements for an ideal separator in LIBs.

A redox-active separator concept was realized by fabricating a bilayered polypyrrole–CNF separator, which provided the necessary insulation and prevented internal short circuits (Z. [74]. The LIB that adopted this redox-active separator exhibited an increased specific capacity and high thermal stability. To address the safety concerns about LIBs, the current challenge is to develop a heat-resistant and flame-retardant cellulose separator. The cellulose-based composite nonwoven separator, with its great flame-retardant and electrochemical characteristics, represents an important advance, via the strategy of replacing the synthetic polymer by a renewable polymer-derived separator that essentially features higher porosity (~15%) [1, 68]. The highly porous structure of the flame-retardant cellulose-based composite nonwoven (FCCN) separator which consists of well-distributed CNFs as a superior reinforcing material [8] results in high electrolyte uptake, which leads to high ionic conductivity due to more electrolyte being soaked up by the FCCN separator, and this facilitates rapid ionic transportation [14]. This FCCN-based separator depicts some special features, which offer advantages over the polypropylene (PP) separator such as improved electrolyte wettability, mechanical robustness and integrity, uniform tensile strength, and better cycling performance in LIBs with a stable charge/discharge behavior. These features in FCCN enable much better safety features, which essentially make the FCCN separator promising for LIBs for consumer electronics. Zhang et al. [84] for the first time reported the use of a commercial rice paper as a separator in LIBs having cellulose fibers. Hu et al. [22] prepared thin and flexible secondary LIBs, where commercial

paper, with macro/microscopic cellulose fibers, functions as both mechanical support and separator with double layer films laminated onto the paper. Overall, cellulose-based separator materials in LIBs, gives high stability, good ion transport, higher tensile strength, good thermal property and wettability.

4.2.4 Cellulose-Based Current Collectors

The current collector works as an electrical conductor which bridges the electrodes and external circuits and provide a support to the coating of the electrode materials. Metal foils are generally used as current collectors in supercapacitors and batteries even though they are expensive and heavy, increase the cost and reduce the mass fraction of the active material in the electrode and in addition, can undergo mechanical deformation in the long term, which can affect the electrochemical stability of the ESD negatively [29]. So, development of lightweight, flexible, and sustainable current collectors becomes very important. In the form of paper sheets, cellulose can be used as the substrates for LIB electrodes in place of the metal foil current collectors [72]. One approach is to deposit a thin layer of a conductive material on the surface of a cellulose sheet, thus converting the insulating paper into an inexpensive and flexible conductive paper current collector [33]. In conventional LIBs, lithium intercalation materials are used in both cathodes and anodes. These electrode materials are usually coated onto a metal foil serving as a current collector and structural support. The technique of coating current collector and electrode materials onto cellulose paper sheets is critical. [23] first exercised a simple Meyer rod coating method to coat carbon nanotubes (CNTs) and silver nanowires onto commercial Xerox papers and achieved sheet resistance as low as 1 ohm per square [21].

5 Conclusion

Cellulosic material has emerged as a feasible solution to ever-depleting resource and environmental pollution. An abundance of nanocellulose from plants and bacteria sources has shown superior mechanical, electrical, mechanical, and optical properties as potential substrates. Over the years, the nanocellulose material has been chemically and physically modified for various energy applications including: (1) the fabrication of nanocellulose-based composite for battery electrodes, solid polymer electrolytes (SPEs) lithium-ion batteries (LIBs), and supercapacitors (SCs) with higher thermal stability and energy/power density; (2) the development of CNC film as conductive nanopaper in the solar cell with superior flexibility, foldability, and bendability; (3) the synthesis of nanocellulose with metals and metal oxide as photocatalytic nanocomposite materials; (4) the modification of nanocellulose with silanes in the preparation of aerogel as CO_2 selective adsorbents; (5) the preparation of highly transparent nanopaper for electronic devices. Various conducting materials such as CNTs, graphene, metal nanowire, and carbon fibers were embedded into

nanocellulose structures to improve its conductivity for excellent electrochemical and mechanical performance. The morphology of the modified nanocellulose also shows the successful fabrication of nanocellulose-based material for energy applications. Besides, the conversion of cellulosic materials into bioenergy products such as charcoal, syngas, bio-oil, and bioethanol also can be produced through thermochemical and biochemical conversion. However, further improvements are still needed through the practical transition from laboratory to commercial scale for cellulosic materials production. A new method and optimization process for producing cellulosic materials with large scalability and low cost is required to achieve the feasibility of nanocellulose-based materials manufacture. The life cycle assessment of environmental aspects of nanocellulose-based materials also must be analyzed to introduce the products in the market. Despite the above challenges, cellulosic-based materials will certainly serve as a powerful material platform for the development of energy materials technology in the future.

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Cellulose and Its Composites in Textiles and Food Industry

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Abstract The usage of synthetic materials has increased environmental contamination to critical levels in recent decades. It will be difficult to restore the eco-equilibrium system's without boosting the usage of natural, environmentally favorable chemicals. The usage of renewable cellulose may help the environment in a substantial way, both directly and indirectly. Because cellulose is a biodegradable, non-toxic, and renewable raw material, its value is linked to sustainable development. Cellulose materials are utilized in a variety of applications in both the home and the workplace. In the food, pharmaceutical, materials, and textile sectors, cellulose, and its composites have long been regarded as critical raw materials. Researchers are very interested in cellulose research in order to produce new goods and to live a comfortable and safe life. This chapter will focus on the most recent cellulose-based materials, their properties, and their applications in the textile and food industries. Future difficulties, research requirements, and viewpoints will all be thoroughly covered.

Keywords Cellulose · Composite · Regular fabric · Engineering fabric · Smart textile · Bioactive textile · Food packaging · Food supplement

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1 Introduction

The global textile industries are facing unprecedented sustainability challenges. Numerous problems, including a growing global population, climate change, water scarcity, a lack of suitable land for the production of fiber, deforestation and biodiversity loss, and non-biodegradable waste management, have combined to cast doubt on the industry's long-term viability and efforts to establish a sustainable circular economy. It is crucial to find new sustainable raw materials and manufacturing processes as well as to develop green and sustainable ways across the whole supply chain of this business. High population expansion necessitates an increase in the consumption of heavy textile fibers, which in turn generates heavy waste. Recently, the demand for textile materials made from bioresource has increased because it can reduce environmental pollution by reducing carbon dioxide emissions and their production does not require fossil fuel resources [1, 2]. As the most significant and readily available renewable resource for textiles, cellulose offers a special material with improved structural characteristics. The physical and chemical modification processes that result in fibers with greater broader properties, which have high commercial value today [3–5].

Cellulose is the most plentiful natural polymer. From the ancient time, cellulosic materials have been used in industries for developing paper and textile. In the last two decades, cellulosic materials have been used in advanced material for electronics [6], nanomaterials [7], construction[1], pharmaceutical [8], cosmetic [9], food [10], coatings and adhesives [5], gaskets, packaging [11], biomedical application [12], etc. Cellulose-based materials specially show great promise owing to their cost-effectiveness, biocompatibility, biodegradability, high mechanical properties, thermal resistance and low cost. Moreover, numerous new materials are explored constantly due to the chemical functionality of cellulose [13, 14]. Everyday different form of cellulose products are developed for all manner of applications in textile industry. In recent years, cellulose fibers have had more yearly demand growth than more established fibers like polyester, acrylic, polyamide, and spandex, in particular of their superior water absorption, softness, and cotton-like attributes. In the last few years, cellulose materials have become a popular food additive due to their unique chemical and physical properties [15]. The use of cellulose in the production, processing, and packaging of food encourages the development of new technology. This chapter provides an extensive survey on cellulose and its composite, their structural and properties, with an overview of applications in textile and food industry. The content can help researchers in the exploration of possible applications of cellulose and its composites, as well as providing ideas for product development in textile and food industries as functional food ingredients, food stabilizer, delivery systems, and biodegradable packaging.

2 Textile Application of Cellulose and Its Composites

In textiles, cellulose is frequently utilized as a raw material to produce final products. It is gathered from various sources and put through several processing procedures, such as scouring cotton and processing bast fibers, in addition to the well-established process for cellulose-based fiber finishing. D-glucopyranose rings joined by β-(1–4)-glycosidic linkages make up the natural linear polymer known as cellulose. It has great mechanical and thermal qualities and is the most prevalent and abundant biomass resource [2, 16]. Natural and synthetic cellulose are two different sources of cellulose. Natural cellulose can be found in a variety of plant, animal, and mineral sources, including cotton, sisal, hemp, flax, ramie, okra, kapok, coconut fiber, bamboo, grass, and PALF. Since different sources of cellulose have varied qualities, they are employed for various applications in the garment industry. Additionally, certain chemically altered cellulose fibers exhibit exceptional strength, brightness, dyeability, and lavishness on par with synthetic fiber made from petroleum sources. Simple biofinishing or biopolishing techniques are used to make the most popular chemically altered cellulose fibers, including rayon, modal, and the more recently developed lyocell. The most popular form of regenerated cellulose produced by the cupro-ammonium method is rayon [17]. Combining the cellulose components with synthetics or other cellulose-based fibers is also utilized to make yarn. Elegant fabrics like satin, modal, jersey, and denim are created from a variety of higher-value cellulose materials, including cotton, linen, hemp, lyocell, rayon, and viscose [18].

Clothing which not only looks beautiful but also feels amazing is appealing to modern shoppers. The importance of garment comfort in determining customer happiness has been demonstrated through studies. These days, a garment's requirements include clothing comfort in addition to style and durability. When worn, clothing that comes into direct contact with the body interacts with the skin in a constant and dynamic way. Such contact between cloths and the human body generates mechanical, visual, and thermal experiences, which eventually rise to perceptions of comfort or pain. According to Slater, clothing comfort is a pleasant state of a person's physiological, psychological, and physical harmony with their surroundings. Psychological, sensory, and thermophysiological comfort are the three main clothing comfort factors. The key determinants of thermophysiological comfort are well-known to be the kind of fiber, yarn qualities, fabric structure, finishing techniques, and wearer situations. Crucial cues to the feeling of state of comfort are sensations that result from the heat and moisture-transporting capabilities of garments. Engineering fabrics that offer the wearer the most comfort requires an understanding of the fabric characteristics that affect temperature and moisture sensations. The denim fabric has undergone advancements to offer new colors and a distinct look and feel, but little is said to have been done to make this enduringly popular clothing more comfortable.

2.1 Regular Fabrics

There are numerous different types of fabrics used in the textile industry for making clothes and other common uses. Fabric is an outcome of the textile industry formed by weaving threads or yarn into a web. By knitting or weaving the yarns together, fabrics that are used for clothing and garments are interlocked. But other fabric-making fibers are also fused together with the application of heat, force, or chemicals. Knitted, woven, and non-woven fabrics make up the majority of classifications of fabrics. There are many distinct sorts and shapes of fabrics, and each type has a unique feel and set of characteristics. Some fabrics are used in the clothing industry to manufacture garments and accessories, while others are used to create cushioning. Here is a list of all the major fabric kinds that are frequently used in the textile industry. Fabrics are categorized into the following list of fabric names according to the yarn that was used and the characteristics of the finished product. Additionally, you may find several fabric kinds here with illustrations that can aid you in understanding the materials and how they are used in various contexts (Table 1).

Cotton Fabric

Cotton is a staple material that is made from the natural fibers of cotton plants. This indicates that it is made up of fibers of various lengths. Cotton's main component, cellulose, a plant fiber that is insoluble and has soft, fluffy qualities, is used to make clothing. In order to generate the yarn, cotton strands are spun together to form soft, enduring garments. Clothing like t-shirts and home furnishings like bed sheets are made from cotton fabric products. The most widely utilized fabric in the world is cotton.

Denim Fabric

The denim fabric has firmly established itself as a choice of "street clothing", which is appealing to people of all ages and socioeconomic backgrounds. More than at any other period in the past, denim mills are investing a significant amount of money in the development of new denim concepts. As a result, all denim makers will play with and achieve new levels of finishing. Since its inception, the product has only ever been traditionally produced with 100% cotton. All age groups favor denim as a distinctive piece of clothing, and because of this, a lot of improvement work has been undertaken in recent decades. These advancements have led to a significant variety of denim varieties being offered to customers today. There are many different types of denim fabric, some of which have names like stretch denim, crushed denim, acid-washed denim, raw denim, and sanforized denim. Stretch denim (denim with Lycra) has recently replaced denim as the preferred type of clothing. In order to allow for some stretchability in clothing, stretch denim usually incorporates an elastic material (like elastane) into the fabric. Denim is a thickly woven fabric created from coarse, indigo-dyed warp yarn manufactured from 100% cotton and gray weft yarn. Traditional denim is a stiff, dense fabric that has a high mass per unit area. Denim

Table 1 Cellulose and cellulose composites used in regular textile fabric

Regular fabric	Cellulose sources/types	Pattern of woven fabric	Advanced Feature	References
Denim Fabric	Regenerated cellulose and its derivatives (modal, Tencel, and bamboo) yarns + viscose	3/1 twill weave (ring yarns used with 2/30 s count in both warp and weft direction)	• Low yarn fineness and hairiness • Comfort clothing with less cover factor	[19]
		To generate a diagonally textured fabric surface, one set of yarns floats over another in 2–5 (often 2–3) sets of yarns at regular intervals	• Comfortable, fashionable, affordable and durable, good abrasion resistance	[20]
		typically made with twill weaves like three-up-one-down (3/1) and two-up-one-down (2/1)		[21, 22]
	A heavy fabric called denim is woven from coarse, indigo-dyed warp yarn consisting of 100% cotton and gray weft yarn			[23, 24]
	100% cotton	It has a gray weft and a dyed warp. The majority of the denim fabric is constructed using a left- or right-handed twill in a 2/1 or 3/1 pattern	• Particularly durable, rigid, and strong fabric	[25]

(continued)

Table 1 (continued)

Regular fabric	Cellulose sources/types	Pattern of woven fabric	Advanced Feature	References
Digital Printed Fabric			• Special designs with excessively small repeat sizes, high resolutions, thin lines, intricate, or delicate patterns • A wide range of colors can be created with digital printing equipment	[26]
Viscose Fabric	The regenerated cellulose fibers	2440 dtex linear density, 1350 filaments, and the twist Z40 for viscose yarn	• Possess high levels of purity, homogeneity, and reproducibility • Soft, delicate, well draped, silky and shiny, extremely durable in a dry condition, and light in weight	[27]
Khadi Fabric	Cotton, silk or wool		• Chemical-free characteristic • Capacity to absorb moisture • 100% natural and therefore, not harmful to skin • Used for both warm and cool weather • Light, soft and subjected to dyeing and printing • Comfortable, inherent strength	[28–30]
Satin Fabric	Satin is frequently woven from fibers like silk, cotton, wool, and polyester	The fabric is constructed in a manner similar to a twill weave and is made from low-twist yarn	• Glossy, smooth, sleek • One side is shiny and other side is dull, high luster	[31]

(continued)

Table 1 (continued)

Regular fabric	Cellulose sources/types	Pattern of woven fabric	Advanced Feature	References
Chenille Fabric	pile yarns made of wool and wool-blend	Different fiber finenesses and yarn types (two-folded ring, sirospun)	• Highly vulnerable to abrasive forces	[32]
Cotton Fabric	Natural cotton fibers		• Lightweight, environment friendly, biodegradable, good mechanical strength, high flexibility, good breathability, abundant, renewable, high porosity, large surface area • Relatively inexpensive, locally available, no skin stimulation toxicity, broad chemical modification capacity	[33]
Jersey Fabric	Cotton, wool, viscose (rayon), polyester and polyamide	The characteristic, tightly woven structure of jersey fabric is produced by the knitting machine by twisting and combining yarn	• Lightweight, considerable stretchiness and close knit, highly absorbent, attractive drape	[34]

(continued)

Table 1 (continued)

Regular fabric	Cellulose sources/types	Pattern of woven fabric	Advanced Feature	References
		There is a right side (face) and a wrong side to traditional single jersey fabric (reverse). On a single bed, it is knitted with a single set of needles. Two sets of needles are used on two needle beds to knit a double jersey fabric. Double-faced interlock jersey fabric has knit stitches on both sides	• Very comfortable to wear, doesn't wrinkle easily, and stretches to fit the body • Breathable, odor-free, cool, and moisture-wicking	
Lace Fabric	Cotton, polyester and nylon, spandex and nylon	Cross or knitting yarn is often woven into the cloth on an open mesh pattern looper by hand or machine	• Decorative textiles has sculpted a sense of luxury and a particular romantic, easy hook wire	[35]
Modal Fabric	Wood pulp based cellulosic fiber	Each yarn produced was converted to twill, cross tuck, cross miss, and single jersey knit textiles	• High tenacity and high wet modulus, air permeability, thermal conductivity	[36]
	Modal fabric is a bio-based from the spun reconstituted cellulose polymer of beech trees	Modal (100%) has a yarn count of 27 for both the warp and weft, and cotton (100%) has a yarn count of 30 for both the warp and weft	• Resist fading and shrinkage even after numerous washings, shrinkage • Resist accumulation of hard water mineral deposits	[37]
	Pulp of cellulosic fiber		• A high wet strength, additional softness, and excellent wear resistance	[38]
Muslin Fabric	Cotton	Hand-woven of finest handspun cotton yarns	• The texture was so fine that the body of the wearer was visible through it • Some varieties of Muslin were so thin and fine that an entire muslin saree made of such fabric could fit inside a single matchbox	[39]

(continued)

Table 1 (continued)

Regular fabric	Cellulose sources/types	Pattern of woven fabric	Advanced Feature	References
		Loosely woven cotton fabric of plain weave technique	• 100% cotton and one of the cheapest fabrics that available around the world • Very good breathable	[40]

is typically made with twill weaves like three-up-one-down (3/1) and two-up-one-down (2/1). Denim comes in enticing indigo blue hues, is created for a multitude of uses, and comes in a variety of quality. Denim is popular among all age groups since it is cozy, stylish, inexpensive, and long-lasting.

Viscose Fabric

Silk is replaced with viscose, a semi-synthetic rayon fabric manufactured from wood pulp. Viscose has a comparable drape and smoothness to silk, giving the fabric a luxurious feel and making it a popular silk alternative. By using chemicals, the wood pulp is transformed into fabric. The fabric is quite popular since it is lightweight, breathable, and absorbent with a pleasant feel. Although the cloth is not naturally stretchy, spandex can be added to it to make it so. As a result, it is clear that the textile industry uses a variety of materials.

Khadi Fabric

Khadi, sometimes referred to as khaddar, is a naturally produced handwoven fabric composed mostly of cotton. Silk and wool are also used to make several kinds of khadi fabric. Khadi cloth has a rough texture that is comfortable to wear both in the summer and the winter. The khadi fabric is now offered in a wide range of variants, prints, and motifs, including block and Kantha prints. Additionally, the fabric is offered in a variety of t-shirts, skirts, and jeans. Modern khadi production is automated as a result of industrialization. Due to this, the production process was sped up, and new cuts and designs of fabric were made accessible. Khadi is one of the most well-known fabric brand names in India.

Satin Fabric

One side of satin is lustrous and the other is dull, making it a soft and silky fabric. This is a product of the satin fabric's weaving technique. Satin is frequently made from silk, polyester, and nylon. Some people insist that satin can only be made from silk because it is thought to be more of a weaving process than a fabric. There are several made and utilized fabrics in the textile industry that resemble satin.

Linen Fabric

Fabric made from the flax plant, known as linen, is durable, very absorbent, breathable, and light-weight. It is a typical fabric used to create bedsheets, tablecloths, towels, and napkins. Additionally, the fabric is utilized as the inner lining of jackets, hence the name "lining." This fabric's light weight allows air to travel through and regulate temperature, making it perfect for summer wear.

Canvas Fabric

It is a strong and durable fabric constructed of heavy cotton yarn with occasional additions of linen yarn. When cotton is combined with other synthetic textiles, canvas, which is typically a plain-weave material, can be transformed into a water-resistant or even water-proof material.

Because of this, canvas might be the perfect outdoor fabric.

Gingham Fabric

Gingham is a plain-woven cotton fabric, or occasionally a cotton hybrid created with colored yarn. Checked patterns that can be produced in a variety of sizes are the product of this procedure. The most popular red-white and blue-white gingham color combinations are among the many dual-color gingham patterns that are available. This fabric has reversible patterns that are similar on both sides. Gingham is a well-liked fabric that is frequently used in shirts, dresses, and tablecloths due to its low cost and ease of production.

Chenille Fabric

Chenille is a soft fabric because it is both a fiber and a yarn. When producing chenille, the threads are purposely stacked high, giving the finished product a fury-like caterpillar appearance. Since chenille is a woven fabric, a range of various fibers, including cotton, rayon, silk, and cotton, can be used to weave it.

Jersey Fabric

A soft, stretchy fabric called jersey was initially created from wool. But at the present, cotton and cotton-based blends, as well as synthetic fibers, are being used to make it. The jersey knit fabric has loops all over one side, which is smooth on the right. Jersey cloth is perfect for bed sheets and sweatshirts because it is light to medium weight.

Digital Printed Fabric

Instead of utilizing outdated traditional printers, it is a method of printing fabrics using digital inkjet printers. When printing on cloth, digital printers are recognized to be more cost-effective and to produce less waste than other techniques. Due to the printing process using a graphic picture, digital printing also produces higher-quality output, which improves printing's overall quality and yields better, more accurate outcomes. It is common to utilize digitally printed fabric for bed sheets, pillow cases, and other items in addition to apparel. Manufacturers and exporters choose it for use in clothing and cushioning since digitally printed fabric is popular for use in clothing as well as other areas like bed sheets, pillow covers, etc.

Lace Fabric

Originally created from silk and linen, lace is a delicate fabric that is now frequently made from cotton thread and synthetic fibers. It is distinguished by its open wave patterns, which are produced using a variety of methods. Most often, lace is used as a decorative fabric to enhance the appearance of garments and home furnishings. Given that it requires a lot of time and effort to manufacture, lace is still regarded as a premium material. There are numerous types of lace fabric available, including fancy lace, GPO lace, embroidered lace, jacquard lace, border lace, narrow fabric lace, etc.

Modal Fabric

The pulp of a beach tree is used to create this semi-synthetic fabric. Another type of rayon is modal, which is more resilient and flexible. To improve its tensile strength and durability, it is typically mixed with other fibers like cotton and spandex. Clothing like pajamas and underwear as well as home goods like bed linens and towels are frequently made of modal. One of the few brands of cloth that is well-known and readily accessible in the market is modal.

Muslin Fabric

The unique sort of cotton cloth with a simple weave is called muslin. In the fashion industry, muslin fabric is employed to test patterns prior to cutting and stitching. Muslin is available in a wide range of weights, from fine sheers to thick sheeting. Muslin is an excellent material to test patterns because it is lightweight and gauzy. As a result, it is utilized to mimic drapery and is simple to sew with. Because of this, muslin is a great material to test designs on in the fashion industry. Mosul in Iraq, once thought to be its birthplace but later shown to be further east, and Dhaka in Bangladesh. Three crucial elements which made Dhaka's muslin unique are the utilization of rare cotton, the fineness of its hand-spun yarn, and the amazing talent of its weavers. The handloom can accommodate any requirement, even for highly demanding fabrics. Weaving is a craft that predates human civilization. Muslin is a low-cost, incredibly sturdy fabric. Muslin is easily dyed for any purpose.

There are numerous different types of fabrics used in the textile industry for making clothes and other common uses. Fabric is an outcome of the textile industry formed by weaving threads or yarn into a web. By knitting or weaving the yarns together, fabrics that are used for clothing and garments are interlocked. But other fabric-making fibers are also fused together with the application of heat, force, or chemicals. Knitted, woven, and non-woven fabrics make up the majority of classifications of fabrics. There are many distinct sorts and shapes of fabrics, and each type has a unique feel and set of characteristics. Some fabrics are used in the clothing industry to manufacture garments and accessories, while others are used to create cushioning. Here is a list of all the major fabric kinds that are frequently used in the textile industry. Fabrics are categorized into the following list of fabric names according to the yarn that was used and the characteristics of the finished product. Additionally, you may find several fabric kinds here with illustrations that can aid you in understanding the materials and how they are used in various contexts.

2.2 Cellulose-Based Engineering Textile

Recent advancement of technology makes it possible to replicate cellulose strands with the highest tensile strength without using risky or labor-intensive chemical processes. Engineering textiles made of cellulose that is flame-retardant, conductive, magnetic, and insulating materials are addressed in this area.

2.2.1 Fireproof/ Flame Retardant Materials

The burning of textiles has long been seen as a serious concern because the majority of fibers and fabrics, which are used often in daily life (such as in the transportation industry, the automobile industry, protective clothing, the military, furniture upholstery, bed linen, and nightwear), are combustible and potentially hazardous materials. As a result, chemicals known as "flame retardants" have been created to reduce the risk of fire by preventing fabric ignition or slowing the rate at which flames spread. Chemistry developed between 1950 and 1980 served as the foundation for the development of flame retardants along with their treatments, formulations, and additive preparations. Some of these currently have commercial relevance due to worries about the toxicological and environmental effects of utilizing such chemical species on textile substrates with high specific surface areas and non-toxic to intimate touch with the skin. The perceived need for improved flame-retardant performance at an affordable price has prompted research scientists and industry to examine increasing the efficiency of currently employed retardants, replacing those where concerns reside with other existing formulations, or employing known chemistry in creative ways [41, 42]. The ongoing search for long-lasting retardant systems that, through enlarged char formation, boost thermal barrier qualities, as well as the use of nanoparticle presence to aid this same process, are notable challenges. Additionally, the growing pressures to replace formaldehyde-free treatments in durable finishes as well as antimony-halogen systems in textile back-coatings are covered.

Because of this, the majority of highly effective halogen or formaldehyde-based flame retardants for fabrics have been restricted or banned from use in commerce over the past 30 years, preferring the usage of phosphorus-containing goods. Three approaches in particular have produced the most intriguing results among the various, new strategies that have been developed and are being deployed [5, 43]:

(i) the utilization of synthetic nanocomposite fibers,
(ii) adding nanoparticles to conventional back-coatings and
(iii) application of nano-coatings to the substrates of fabric.

Up until now, the primary focus of the nano coating strategy has been the use of ceramic protective layers or flame-retardant species, either separately or in combination. Thus, it has adopted a variety of techniques, including plasma deposition, sol–gel and dual cure procedures, layer-by-layer assembly, and nanoparticle adsorption.

The era of flame retardant materials may be changing owing to proteins and nucleic acids. The future of textile flame retardation may involve biomacromolecules, according to recent research [44]. Whey proteins, caseins, and hydrophobic proteins, as well as deoxyribonucleic acid (DNA), have lately demonstrated unexpected flame retardant/ant-suppressant properties when deposited on cellulosic or synthetic substrates, such as cotton, polyester, or cotton-polyester blends [3]. However, a large-scale approach recently developed that is based on the extraction and purification of DNA from salmon milt and roe has made DNA availability competitive with that of other chemicals, notwithstanding its high cost at the moment. This method is based on the use of some of these biomacromolecules (such as caseins and whey proteins) as

waste or byproducts from the cheese and milk industry. These biomacromolecules can be incorporated into textiles either by an impregnation/exhaustion process (which is representative of a standard textile finishing process) or through a layer-by-layer technique, beginning with aqueous solution/suspensions and so utilizing a substantially greener approach. Research is still being done to determine how these biomacromolecules provide flame retardancy to fabrics. The chemical composition of these green macromolecules and their interactions with the underlying fabrics, which, when heated or exposed to a flame, favor the production of a stable and protective char (i.e., a carbonaceous residue), which prevents the exchange of oxygen and combustible volatile chemicals, appear to be a factor in the textiles' flame resistance. Due to their ability to influence the pyrolysis of cellulose toward the formation of char, caseins and hydrophobics which both include phosphate groups and disulfide units have been examined as effective flame-retardant systems for cellulosic substrates.

The ability of whey proteins to create protective coatings on cotton, which has a high capacity to absorb water vapor, has also been demonstrated. This finding may help to explain the increased flame resistance of the treated fabrics. DNA behaves differently from proteins because it has all three essential components of an intumescent formulation in a single molecule. Charring and foaming at the burning polymer's surface produce intumescence, which shields the underlying material from the effects of heat or flame. Since it may stop a polymeric material's self-sustained combustion, intumescence is seen to be the most effective method for replacing halogen-based flame retardants. Because of the nitrogen-containing bases (guanine, adenine, thymine, and cytosine), which can release ammonia, the phosphate groups, which can produce phosphoric acid, the deoxyribose rings, which serve as a carbon source and blowing agents, and the nitrogen-containing bases (guanine, adenine, thymine, and cytosine), which act as blowing agents, DNA-treated cotton fabrics have even attained. All of the aforementioned methods are still being researched despite having tremendous potential in the field of flame retardancy. Currently, one difficult question about the application of biomacromolecules as flame retardants revolves around the potential for scaling up this technology, which is a crucial factor for evaluating its future industrial development. The great efficacy of these bio-treatments, along with the safety and environmental concerns they raise, point to a new direction for the creation of novel flame-retardant finishing systems for textiles in the near future. The procedure for effectively modifying cellulose to make it flame-retardant is depicted in the preceding image (Fig. 1).

2.2.2 Conductive Materials

Electrically functionalized materials with the benefits of flexibility, elasticity, and wearability are used to create conductive fabrics. Due to these properties, conductive fabrics can now be used to create wearable sensors, textile-integrated batteries, and fabric-based energy storage devices. Figure illustrates many applications for conductive textiles. Health care, the military, and those employed in the defense industry are the main end consumers of conductive textiles. By weaving and knitting conductive

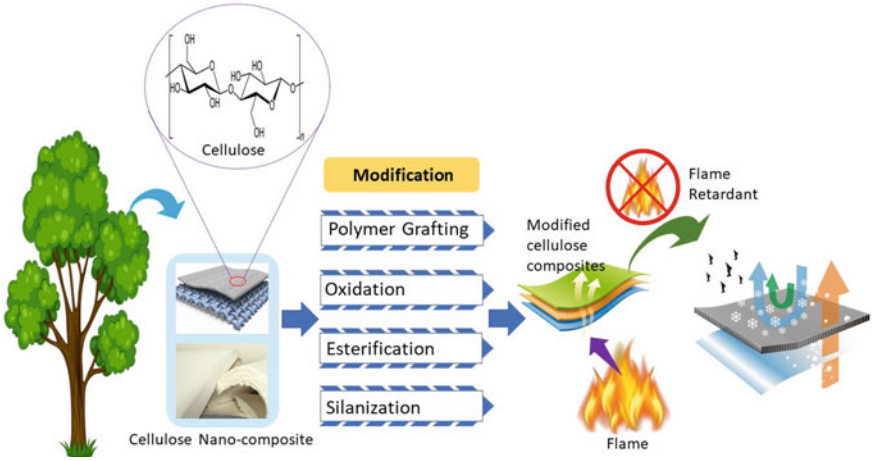

Fig. 1 Cellulose-based flame-retarding materials

threads into fabric or by manufacturing conductive polymers and applying them to cloth, conductive fabrics can be created.

Conductive polymers have extended orbital systems along their conjugate backbones, such as polypyrrole, polyaniline (PANI), and polythiophene [45, 46]. Due to their distinctive structure, conductive polymers are lighter than metals and have higher corrosion resistance. PANI has received the most attention among the many conductive polymers due to its excellent chemical stability, excellent electrical conductivity, and simplicity of synthesis through the in-situ polymerization of aniline. PANI is regarded as a useful material to generate conductive fabrics since it may be polymerized onto cellulose to create conductive fabric with outstanding physical features, like flexibility and biodegradability. While BC possesses a three-dimensional nanostructure with pronounced biocompatibility and purity, MC is produced from chemical cellulose without sacrificing biocompatibility. The idea of creating conductive BC-PANI by polymerizing aniline with BC was investigated in numerous investigations [47] (Fig. 2).

Smart Textile Materials

In order to secure the worker's safety, protective garment use is increasing. The utilization of smart materials that immediately respond to inputs from the environment and the human body by undergoing major, often reversible physical, chemical, and biological changes worry the researcher. The protective clothing that workers are currently using is distinguished by identical protective qualities across their entire surfaces that are tuned to the level of thermal exposure that is allowed. Steel mills and the metallurgical industry both have thermal dangers. Smart thermal protective equipment for such work areas should therefore adapt its protective characteristics to the level of dangerous variables. Such clothing ought to be able to sense the existence of a thermal stimulus from the environment instantly and react to it by going

Fig. 2 Use of conductive smart textiles in different ways

through a reversible physical change that involves increasing its thickness and, as a result, increasing its resistance to heat. However, the garment should have a minimum thickness while a worker is not exposed to temperature variables. While the worker is outside the high-risk area linked to the presence of thermal variables, this will assure a greater level of garment aesthetics. Shape memory alloys (SMAs) are intelligent materials with a big potential to accomplish this [48]. These materials are capable of spontaneous and reversible form changes when exposed to temperature stimuli. This thermoelastic martensitic transformation, which is accompanied by heat exchange, is what causes the shape memory effect. Austenite and martensite phases are where the transition occurs. The two-way shape memory effect (TWSME), which occurs from properly carried out thermomechanical treatment (TT), is a significant characteristic of SMAs that can be employed in smart protective equipment. After cooling to the temperature required for the alloy's low-temperature phase, the SMA element that had one shape in the high-temperature phase takes on a different shape. This implies that the element with TWSME can assume two shapes: one at high temperature and another at low temperature. Furthermore, the change between the two shapes

can be reversed. In-depth application research in textiles and clothing is focused on SMAs' capacity to alter their shape, size, or internal structure in response to a specific stimulus. Because of their ability to produce intricate three-dimensional actuation motions due to their hierarchically ordered structure, active knits made of SMA wire, for instance, offer a significant potential for usage as novel actuators. It is crucial to note that various smart textile materials with SMA elements require different preparations depending on the application [42]. This has to do with choosing and training SMAs, picking fabrics, and choosing an integration technique. As a result, each application is different and needs to be founded on a study of the circumstances at the specific work stand.

Magnetic Materials

This section discusses the characteristics of magnetic fibers and the potential applications for using them to create textile magnetic elements. In addition to their inherent textile capabilities, magnetic fibers fall under the category of multifunctional fibers since they possess additional characteristics that broaden their potential applications in textile products [49]. The type of magnetic material (the filler) present in the fiber matter as well as the filling level affect the properties of magnetic fibers. The amount of grains of magnetic materials inserted into the fiber also affects its mechanical characteristics. The creation of textile magnetic coils, the fundamental component of magnetic circuits, is possible using magnetic fibers. Electromagnets, which serve as the building blocks of electromagnetic actuators, as well as inductive gauges and transmitters all make use of these circuits. Ferromagnetic nanoparticle powders are incorporated into the fiber matter during fiber synthesis to create magnetic fibers. As a result, the ferromagnetic is incorporated into the fiber, which transforms into a macroscopic, monolithic substance known as a composite because the polymer (the matrix) and the powder filler form a discontinuous phase. These composites are also known as electronic composites because they are widely used in the construction of MEMS (micro, nano, and electromechanical systems) and bio-MEMS (BioMEMS). The first textile technology we used to create fibers with magnetic characteristics was the Lyocell method [50]. Utilizing concentrated cellulose solutions in N-oxide-N-methylmorpholine, this technique produces fibers (NMMO).

Powered modifiers with hard and soft magnetic characteristics are added to the spinning solutions to provide a stronger magnetic effect. One of the most effective ways to develop novel fiber qualities is through the modification that takes place during the preparation of the spinning solution because it allows the distribution of the modifier particles throughout the whole volume of the fiber. Contrary to methods based on surface processing, enclosing the modifier particles in the cellulose fiber matter ensures the stability of the modification effect. By incorporating the right modification components into the fiber, it is possible to achieve a variety of results, such as improved electrical conductivity, decreased combustibility, shielding capabilities, or UV radiation conversion, as well as the ability to create fibers with sensory characteristics for a variety of parameters.

Insulation Materials

The earliest type of insulation, cellulose fiber, is still used in new and existing homes to insulate enclosed existing walls, unfinished attic floors, and open new walls [51, 52]. It is largely created from recycled paper fiber and is produced by a number of companies. With the help of these tiny particles, an insulation material may be created that fits most places without affecting the finish or structure. Power transformers employ it because of its exceptional thermal stability. Such equipment is the focus of many researchers' attention because to the high working temperatures that they exhibit. The usage of the cellulose insulating material expanded as fire retardant was added to it. Compared to materials made with mineral fibers, the materials' sound-absorbing qualities were also good [52].

2.2.3 Cellulose-Based Zeo-Textile Materials

In geotechnical applications, such as the building of roads, drains, port works, and breakwaters, as well as for land reclamation and many other civil engineering uses, polymer fabrics known as geotextiles are utilized. One of the technical textile market's fastest-growing segments, geotextiles is anticipated to continue rising in the future. Although synthetic fibers currently dominate the woven geotextile market, using natural fibers is still important, especially in developing nations. Additionally, more trustworthy technical information and design approach for woven geotextiles will be provided through the standardization of several attributes and test procedures. Because of this, woven geotextiles will carry out their intended purposes more successfully during the course of the project. Numerous building and design issues can be effectively resolved by combining the mechanics of woven cloth and soil. However, for this to work, civil engineers and textile specialists must have a thorough understanding of one another.

2.3 Cellulose-Based Bioactive Textile Materials

Textiles made of bioactive materials are those marketed as protecting the consumer's health and hygiene through their fundamental functionalities. Cotton-based textiles have special uses in medicine and healthcare because of benefits including biodegradability, biocompatibility, softness, affinity for skin, and sweat absorption. However, due to their enormous surface area and capacity to hold moisture, cotton fabrics can serve as a favorable environment for the growth of microbiological (bacteria, fungi, algae, viruses, mold, mildew, yeast, etc.). Considering optimal conditions such as humidity, temperature, filth, receptive surface, perspiration, food products, and warmth, the growth of microorganisms on textiles imposes a variety of adverse effects not only on the textile but also on the user. The results include the development of a disagreeable odor, stains and discoloration in the fabric, a decrease in the

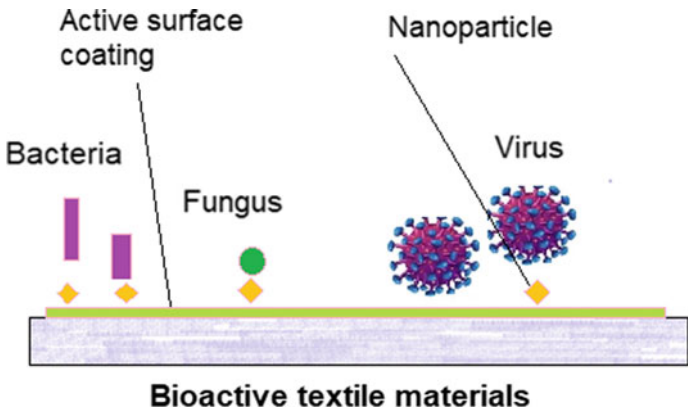

Fig. 3 Bioactive rextile materials

mechanical strength of the fabric, and a higher probability of contamination. To give textiles antibacterial properties, a variety of substances are being used, including synthetic ones like triclosan and cationizing agents like quaternary ammonium salts, metals and metal salts (silver, zinc, and copper), oxidizing agents like halogens, aldehydes, and peroxy compounds, amines like biguanides and glucoprotamine, antimicrobial dyes, naturally derived antimicrobials like chitosan and essential oils [53–56]. The textile industry is encouraged to adopt natural goods as a result of changes in consumer preferences for them over synthetic ones. Propolis is a natural product made from a combination of resin and beeswax from various tree species that honeybees collect from important plant parts, mainly from flowers and leaf buds. Bees utilized propolis as a protective substance against illnesses and parasites as well as to seal off the apertures of the hives to prevent air, dead insects, germs, and mold from entering the hives. The antibacterial, antifungal, antiviral, anti-inflammatory, liver protecting, antioxidant, and allergenic effects of propolis are well recognized. Similar to propolis, beeswax is composed primarily of esters of higher fatty acids and can vary in composition according on the sources and places from which it is harvested. Chitin and chitosan are polysaccharides that are chemically similar to cellulose and differ only in whether nitrogen is present or absent (Fig. 3).

2.4 Cellulose-Based Water Repelling Materials

A material must have a low contact angle hysteresis and an apparent water contact angle of greater than 150° in order to be classified as super hydrophobic, or water repellent. It is not difficult to identify materials that display this; in fact, nature provides a number of great examples of ultra-hydrophobic surfaces. Hydrophobic plant leaves can be found all throughout the planet, including on animal tarsi, gecko palms, and even the shells of some desert beetles. The major elements that influence

a material's hydrophobicity are its surface roughness and surface energy, according to research on biomimicry and other attempts to create artificial super hydrophobic surfaces. Electrospinning has drawn a lot of interest because of its ability to produce fibers with a variety of properties and an ever-increasing range of surface roughness. In order to achieve a super hydrophobic surface, roughened electro spun fibers were coated and changed. In order to research the hydrophilic to hydrophobic transformation via electrospinning for the application such as textile, membranes, and filters, cellulose acetate (CA), low-cost renewable natural polymers has been used. Each glucose module structure has a polar unsubstituted hydroxyl group that, depending on the degree of substitution, requires that it exhibit hydrophilic qualities. The apparent water contact angle for electro spun CA fiber mats is 154 degrees. It is feasible to increase the production of cellulose fibers with water-repellent properties in order to outlaw synthetics derived from petroleum for use in outdoor garments and create a closed ecological loop [57].

2.5 Cellulose-Based Self-Cleaning Surface Materials

The butterfly wing and certain plant leaves, such as cabbage and lotus, are examples of self-cleaning technology, which is one of the many advances that are currently available in the globe. It will be useful to give natural fibers high-performance properties in order to decrease the function of water absorption by natural fibers and/or water penetration on/into fiber surfaces [ref]. Self-cleaning materials have many uses in various industries, including washing windows, solar panels, cement, etc.; this technology has drawn a great deal of attention. Self-cleaning coatings are being developed in textiles in an efficient and environmentally friendly manner to offer a number of applications for various advantages, such as reduced operating costs, the elimination of tiresome human labor, and time savings during the washing process. The enhancement of tightly packed structure to get rid of water droplets that contain contaminants makes a hydrophobic and/or superhydrophobic film coating on fabric surfaces an efficient self-cleaning method [58, 59].

3 Application of Cellulose and Its Composites in Food Industries

In several food businesses, celluloses and composites are commonly used. Cellulose and its derivatives are among the most common compounds in nature. They may be incorporated into food to boost its nutritional content and are both ingestible and biodegradable. It is also well recognized that cellulose has sensory and organoleptic characteristics, including color, appearance, scent, flavor, and taste. It helps to reduce waste and synthetic material-based packaging. It requires less packaging material due

to its small weight. The incorporation or encapsulation of several organic antibacterial and antioxidant compounds is straightforward. In the food sector, biopolymers like cellulose are employed as food coatings. The application of bioactive edible coatings on food surfaces is growing in popularity. They are antibacterial, which allows them to prolong the shelf life of food and keep it fresh.

The whole world is currently experiencing severe food shortages, particularly in third-world nations, and the food that is available is frequently of poor quality due to subpar processing and an inadequate storage facility. Food items must be properly prepared, packed, and secured to reduce the danger of contamination and deterioration to prolong shelf life and enhance quality. To assure the shipping of foodstuffs to other locations and their preservation for a long time, the adoption of sustainable, affordable, and lightweight biobased materials might be a suitable choice. The goal of integrating various technologies into food technology is to improve food's nutritional value, safety, and lifespan. The advancement of a new era of products and services with enhanced qualities for food packaging is currently of the highest significance. The food industry has extensively investigated nano-cellulose, a multifunctional material with distinct structural, Physico-chemical, mechanical, thermal, and biological characteristics, for a variety of applications. To fulfill the need for employing it as food packaging material and nutritional assistance, food additive, and emulsion stabilizer, this chapter addresses the benefits and difficulties of nanocellulose in food technology, as well as its biocompatibility by surface treatment and in vivo introduction of reinforcing materials. The introduction of effective packaging employing biodegradable polymers and antibacterial compounds is also discussed as a novel and alluring method in food technology to stop the growth of microorganisms and ensure sustainability, authenticity, and food integrity.

The primary issue of environmental preservation has resulted in an increase in the necessity for products made from natural resources in recent years. Nanocellulose is a good potential replacement for traditional materials produced from non-renewable resources, and it has the potential to expand the boundaries of this field. This is due to a combination of intrinsically attractive cellulose characteristics and intriguing aspects of nanomaterials. Nanocellulose is used in a wide range of industrial applications, including bio-sensing, sensing, and in different aspects of electrical, medicinal, and mechanical reinforcement fields. As one of the key drivers of growth for the worldwide nanocellulose market, this book chapter focuses on the latest uses of nanocellulose in the food industry. The role of nanocellulose in the development and sustainability of packaging as well as dietary supplements, food preservatives, natural functional components, and as substances and strengthened agents is addressed. To provide further clarity on the features of nanocellulose for the desired food applications, several sources of cellulose, its chemical and structural components, as well as the categorization of nanocellulose, are presented.

3.1 Food Packaging

Incorporating nanocellulose into the matrices of gelatin and starch for replacing polymer-based food packaging applications was the subject of comparative research. The findings indicated that raising the nanocellulose content to 10% increases tensile strength while reducing elongation at break. Additionally, the composite improved the ability to preserve food for about 15 days. [60].

Nanocomposite films made of jute cellulose nanofibrils and hydroxypropyl methylcellulose were created for possible uses in packaging and transdermal medicine administration. By adding 1 weight percent of cellulose nanofibrils, the films' storage modulus and tensile characteristics improved. According to the data from in vitro drug release, the concentration of cellulose nanofibrils in the nanocomposite, which has been identified as the most effective formulation for packaging and transdermal drug delivery systems, causes a decrease in drug release [61].

Silver, copper oxide, or zinc oxide nanoparticles were synthesized for the preparation of cellulose and microfibrillated cellulose (MC) from cotton linter to create antimicrobial hybrid nanomaterials. Due to their potent antimicrobial property against *E. coli* and *L. monocytogenes*, cellulose/metallic nanoparticle hybrids can be employed as nanofiller for the making of antibacterial packaging materials [54]. Antibacterial latexes were prepared by emulsion polymerization with cellulose and their incorporation with acrylate which are hydrophobic and macromonomers with antibacterial characteristics. High potency against *E. coli* was observed while using these latexes [62]. Saha et al. (2018) introduced a kind of packing substance by modifying montmorillonite with cellulose acetate butyrate, benzyl trimethyl ammonium chloride, and poly (ethylene) glycol [63]. Using a homogenizer, foams of cellulose nanocomposite were created, and they used treated montmorillonite of which the surface was modified to optimize the mechanical and barrier characteristics as well as the thermal insulation performance while also improving the properties of the cellulose matrix. The nanocomposites loaded with a little amount of treated montmorillonite have dramatically improved thermal, mechanical, and barrier capabilities, making them a potential replacement for polystyrene trays in the packaging of dry foods [64]. Poly (lactic acid) was used to form nanocomposite with cellulose nanocrystals to obtain a food packaging material and to improve the antimicrobial activity, AgNPs were incorporated, and it showed prominent results against microorganisms [65].

ZnO was used to form a composite with cellulose to introduce the same idea against different microorganisms, and the composite showed improved antimicrobial activity against the *S. aureus* and the *E. coli* and the diameter of the zone of inhibition were 48.8 and 45.5 respectively [66]. The use of cellulose-reinforced poly(lactic acid) (PLA)-based sheets as material for food packaging has attracted a lot of interest. However, numerous studies looking at the mechanical, thermal, antibacterial, and barrier characteristics, as well as the biodegradability and ability to compost in these composite materials, have not taken into consideration the semi-crystalline behavior of both bio-based hydric polymers. This review presents a critical evaluation of the

body of literature that exists in this field, focusing primarily on studies conducted over the past five years on the interactions between these immiscible polymers' crystalline and amorphous regions, "soft" and "hard" sections, and blends of these materials. This assessment has also made recommendations for future work that should be done to address the numerous problems that are now in existence. The papers we've looked at show us that to extend food's shelf life, prevent adulteration, and create more convenient food packing materials for modern society, the emerging innovations in the progress of these substances as food packaging will be centered on shape memory, pH-sensitive, and active films. Different approaches were noticed to prepare highly modified composites. One of them was grafting PLA into MC to improve compatibility. Nanocomposites with high transparency were prepared by blending Polyethylene glycol (PEG) into PLA/MC composite, and the final product was obtained with outstanding barrier characteristics and biodegradability. These composites also showed excellent disintegration while applying compost conditions and an impressive barrier to oxygen. Another approach was reported to modify stretchability by PLA–PHB–CNCs–ATBC, while some degree of blocking effect against UV was also noticed [67]. The researchers reported that they used natural resources for obtaining cellulose, thus a packaging material with zero toxicity that was prepared at a very low cost. To improve the oxygen barrier characteristics, another research work was reported mentioning the incorporation of nanoclay and PLA in which they used nanocellulose as a reinforcing agent to obtain a composite film [68]. An approach to prepare composite films by using coconut husk to prepare cellulose nanofibrils (CNF) which were further used to prepare the composite with poly (vinyl alcohol) (PVA). They used the oxidation method which was mediated by TEMPO for the preparation of the composite. The thermal stability and tensile strength of the composite films have been significantly improved by the addition of 3% CNF to PVA for preparing these biodegradable films. It demonstrated the possible use of CNF as filler in food packaging [69]. In addition, bioactive elements found in cellulosic materials, like antioxidants and antimicrobials, may be used to improve the quality and shelf life of food products by being added to food packaging [70]. Polylactic acid (PLA) and cellulose from durian peel were combined to create a natural fiber composite. The butylated hydroxytoluene (BHT) added to these two mixes' bio composites improved the food's capacity to withstand oxidation, demonstrating their potential as antioxidant-active packaging [71]. The mechanical characteristics of durian rind-derived cellulose for application in ecologically friendly film for food packaging were then examined by G. Zhao et al., 2019 [72]. The cellulose is capable of forming a transparent, smooth film with exceptional heat resistance qualities and high tensile strength. The biodegradability of the film is one of its distinguishing features, and studies have shown that it dissolved completely in the soil in just 28 days. Ghaderi et al., 2014 found that cellulose nanofiber with a diameter of 39 nm generated from sugarcane bagasse has the potential to be used in food packaging [73]. It can be utilized in food packaging as a wall of the protective film due to its high tensile strength (up to 140 MPa). It was asserted that CNC manufactured from paper mulberry (*Broussonetia Kazinoki Siebold*) bast pulp has a promising future as a biodegradable food packaging component. To construct composite films,

agar was mixed with 50–60 nm-sized nanocellulose produced by acid hydrolysis (47 percent H_2SO_4). The outcomes demonstrated that adding CNC to agar significantly enhanced its mechanical properties (tensile strength) and water vapor permeability [74]. Rachtanapun et al., 2015 used mulberry paper waste utilizing the etherification technique to make CMC in a different investigation [75]. The physical properties of the packing film had been improved by the mixture of glycerol and CMC. Similar evidence was shown by other CMC application research that was published by Suriyatem et al., 2018 [76]. A biodegradable film with outstanding mechanical properties was successfully created using rice starch and CMC from durian rind in a 50:50 ratio. Using the casting method, arrowroot starch (AA)-based films containing cellulose nanocrystals (CNCs), carnauba wax nanoemulsion (CWN), and essential oils (EOs) from Cymbopogon martinii (CEO) and Mentha spicata (MEO) were created. These films were then evaluated for their water barrier, thermal, tensile, microstructural and optical properties, as well as their in vitro. While the addition of either EO reduced the transparency and had an impact on the microstructure of the AA/CWN/CNC/EO nanocomposites, the addition of CNCs lowered the moisture content and water vapor permeability of the AA/CWN/CNC film. The addition of MEO and CEO increased the films' thermal stability and offered outstanding defense against fungi that degrade fruit. These AA/CWN/CNC/EO films show tremendous potential for usage as coating materials or active food packaging due to their superior barrier qualities against fungus growth, water vapor permeability, and visible and ultraviolet light [77]. Due to the sustainable and ecological beneficial properties of these polymers, the fabrication of biopolymers suited for food packaging applications is now an important topic of research around the world. By adjusting the proportion of the hydroxy alkanoates, biodegradable polymers produced by microbial fermentation, particularly polyhydroxyalkanoates (PHAs), which utilize inexpensive biomass sources, may be tailored to include desirable characteristics for various applications. To improve the qualities of biopolymers like polyhydroxyalkanoates while maintaining their biodegradable nature, nanocellulose can be used as a special filler material. When incorporated into the polymer matrix of polyhydroxy butyrate (PHB), nanofillers like cellulose nanocrystals (CNC) can enhance the biopolymer's physical, barrier, thermal, mechanical, and rheological characteristics. However, PHB, which comes from a microbiological source, is hydrophobic in nature, whereas CNC is hydrophilic. This restricts CNC's ability to disperse in the polymer matrix, which may have a negative impact on the characteristics of the resultant nanocomposite. The appropriate concentration of CNC, excellent for enhancing the characteristics of biopolymers, has been found to be 2%, while larger percentages cause polymer breakdown or the agglomeration of nanoparticles during processing. With an emphasis on PHB derivatives in particular, this chapter's broad introduction to polyhydroxyalkanoates and CNCs comes first. The next section contains a thorough overview of PHB–CNC nanocomposites, with a focus on the possible use of these materials in food packaging. We contrast the various methods now in use to create PHB-CNC films, and we present a method for dispersing CNCs into PHB that is both efficient and affordable [78].

3.2 Food Coating

Recently, we got a report about using cellulose nanofibril as a protective coating in food packaging [5]. To cover and shield a plant, fruit, or vegetable, they created an edible composition including CNFs in amounts up to 1 weight percent and 0.1 weight percent nano-calcium carbonate (NCC). When compared to uncoated goods, the plant, fruit, and vegetable coated with CNFs showed less moisture loss, gas exchange, and leaching of useful food substrates (such as anthocyanins). Foods were also shielded from UV deterioration by CNF coating. The UV light transmittance of the CNFs-based films ranged from 7.2 to 27.3%, and the addition of NCC further decreased the transmittance. After being exposed to UV light and stored, the CNFs-coated apples revealed a much higher color intensity (chroma). Additionally, the CNFs covering minimized food weight loss while thawing. For example, the weight reduction of CNFs-coated sliced apples after thawing was around 17%, which was less than the weight loss of uncoated apple slices, which was about 21%.

3.3 Delivery System/Carrier

In food science and engineering, nutrient loss and active component inactivation have been major challenges [79]. First off, during food preparation, high temperatures, low pH, and mechanical forces readily decrease nutrients and active ingredients. Additionally, some food items degrade under unfavorable conditions while being transported and stored [80]. Additionally, a significant reduction in the amount that enters the intestinal system is caused by the fact that certain nutrients (water-soluble vitamins) and active components (probiotics) can be destroyed by gastric juice and bile [81]. Building carriers known as microcapsules and enhancing the distribution mechanism are efficient ways to address the issue [82]. By combining natural or synthetic polymers with microparticles, microcapsules are a type of transportation system. Most CNC-based carriers currently in use were created with future biological uses in mind. Abo-Elseoud et al., 2018 hypothesized that an increase in carboxylic groups on the CNC surface may slow the drug's release [83]. Repaglinide, an anti-hyperglycemic medication, was tried to be delivered using chitosan/CNC nanoparticles. The findings demonstrated that the medication diffused and was released through the nanoparticle matrix following the Higuchi model of release kinetics. Additionally, methacrylamide-modified CNCs isolated from bacteria have demonstrated potential as nucleic acid carriers [84]. Even after the complete complex of nucleic acid with the modified CNCs, more research was necessary to determine the effectiveness of the transfection.

3.4 Food Supplements

3.4.1 Thickener

CMC may have connectivity that hardens and stop the engagement of the fat with stomach contents [85]. In comparison to 0.7% XG and 1% LBG, a lower BC concentration of 0.1% was needed to achieve the same yield stress, suggesting that BC may be considered a viable alternative thickener for food applications [86]. It is possible to deduce from CNCs' rheological characteristics that they might be used as a food thickening. A greater viscosity resulted from the thickening effect, which typically happened when the CNC concentration reached the over-lap percentage and CNCs began to interact with one another and create an intertwined matrix [87]. They claimed that CNCs worked well as a thickener in the supernatant of the chitosan/guar gum hybrid. The supernatant's fluidity rose by 27% when 3% CNC was added. Hydrogen bonding between the hydroxyl groups of chitosan, guar gum, and CNCs was thought to be responsible for this development [87]. Starch is used as a thickener, emulsifier, bulking agent, or stabilizer in the food business. But the longevity of food components is always impacted by modern food production [88]. Because CNF from brown algal waste assimilates casein micelles via hydrogen bonding to produce a flimsy mucilaginous structure, they demonstrates excellent thickening activity in milk. The MTT test verified the brown algae CNF's viability and excellent biodegradability. This characteristic creates a brand-new method for creating bioavailable CNF with a substantial ratio of aspects for use as a food thickening agent [15].

3.4.2 Emulsifier

Sanchez-Salvador et al., 2019 looked at the possibility of producing cellulose microfibers that might help regulate oil-in-water (O/W) emulsifiers without the use of chemicals. According to the results, it was concluded that the 40/60 proportion of sunflower oil-in-water dispersion at a concentration of 0.75% had been effectively sustained by cellulose microbeads recovered from cotton twines by a high-pressure homogenizer [89]. The emulsion created, according to scientists, may be utilized to create reduced-calorie cookie goods. The baked goods contain a low quantity of saturated fats and a higher amount of dietary fiber when equated to those other conventional cookies, according to the nutritional value assessed in this study.

MFC of mangosteen waste was proven effective in stabilizing the oil-in-water emulsifying agent. Winuprasth and Suphantharika conducted more research on the characteristics and capacity of MFC derived from mangosteen rinds [90]. It was discovered that the percentage of MFC has a significant impact on the durability of a microemulsion. It was discovered that the 10% soybean oil-in-water microemulsion has prolonged shelf sustainability for up to 80 days at concentrations greater than 0.50% of MCF. Pornsuda Choublab examined the use of nanofibrillated cellulose (NFC) from mangosteen as an emulsifying agent in mayonnaise in light of the physical and chemical qualities noted above. In place of the egg yolk, NFC was introduced to the mayonnaise recipe at concentrations of 5%, 7.5%, and 10%. The possibility of NFC as a spontaneous emulsifying agent has been demonstrated by the improved cognitive in the quality and shelf life of mayonnaise to 8 weeks [91].

The cellulose nanocrystal (CNC) from pistachio shells has been discovered by Kasiri & Fathi, 2018 to have high promise as a naturally derived emulsifying agent [92]. CNC is made from pistachio shells that were hydrolyzed in acid, measuring 68.8 20.7 nm in diameter and 79.4% crystalline structure. At days 0, 14, and 28, the sustainability of the oil-in-water emulsion was assessed after the addition of the CNC at a dosage of 0.1–1.5%. It demonstrated that the greater CNC there was, the more stable the emulsions were under heat, stress, and storage conditions. The findings supported CNC's amazing potential as a bio-disposable emulsifying agent in the production of food.

Costa et al., 2018 noticed a similar trait in banana peel cellulose fibers, which showed promise as a stabilizing agent for oil-in-water emulsifiers. It can act as a superb shield preventing droplet agglomeration, extending the emulsion's shelf life as a result [93]. In a different investigation, Tamayo Tenorio et al., 2017 found that adding sugar beet leaf cellulose to a combination of sunflower oil and water produced a stable Pickering emulsion. It was discovered that the cellulose in emulsions, due to its tiny size and high content, accumulated and formed a solid, thick layer between the oil and the water [94]. This layer served to lower the interfacial tension, improving the stability of the emulsion. As a Pickering emulsifying agent, cellulose generated from microorganisms was also discovered to have a promising prospect in addition to cellulose taken from vegetable sources. When subjected to ecological problems over time, the great integrity of microbial cellulose aids in the creation of a reliable system. The capacity of bacterial cellulose (BC) to stabilize olive oil-in-water emulsions at various pH levels, temperatures, and ionic strengths was studied by Paximada, Tsouko, et al., 2016. When used as a Pickering emulsifier, the cellulose produced by the *Komagataeibacter sucrofermentans* DSM 15,973 bacterium showed the best stability at a concentration of 1% weight and retained its stability while being exposed to variations in pH, temperature, and ionic strength [95]. These findings concur with those made by Zhai et al., 2018, who found that Pickering emulsion stability is unaffected by changes in temperature or time. 15% wt. was able to be stabilized at a low concentration of BC (0.05%) for 4 weeks of a peanut oil-in-water emulsification at pH 7 [96].

Pickering emulsions are firm, particle-stabilized emulsions that often offer a more durable structure than conventional surfactants. Due to their characteristics of nanometer scale, biodegradability, biocompatibility, and processability, bio-based components from sustainable resources, like micro- and nanofibrillated cellulose, may present new options for Pickering emulsions in the coming years. The objective of this study was to create oil-in-water (O/W) Pickering emulsions utilizing cellulose microfibers (CMF), which were mechanically processed by a high-pressure homogenizer from cotton cellulose twines. The oil-in-water pickering emulsions were created by combining edible oil (sunflower oil) with water that contained CMF at a maximum concentration of 1.0 wt% to create emulsions with various oil-in-water ratios. A measurement of the isolated emulsifying phase's apparent viscosity was made. Results demonstrated the viability of creating and sustaining Pickering emulsions using modest concentrations of CMF, with the viscosities of the emulsifying phase rising 60–90 times in comparison to the sunflower oil, with a shear rate of 1 s^{-1}. Conceptual dietary information for the emulsifiers was also computed and contrasted to other lipids used in meals, demonstrating that they might serve as a viable reduced-calorie item that also contains dietary fiber and can take the place of trans and saturated fats in diets [89].

3.4.3 Calorie Reducer

The emulsion created, according to scientists, may be utilized to create reduced-calorie cookie goods. According to the study's assessed nutritional content, the cookies had a higher level of dietary fiber and less saturated fat than other conventional baked goods [89].

3.4.4 Functional Food

BC, dry foods, and medications (powdered) with 15–65 weight percent of nanocellulose and 85–35 weight percent of a saccharide (those are soluble in water) to avoid nanocellulose aggregation Because of its lack of digestibility, it encourages favorable physiological effects such as laxation, blood cholesterol reduction, gastrointestinal complications, and blood sugar reduction. This makes dietetic meals more appealing [11, 97].

3.5 Food Additives

Today's consumers favored products with organic food products and less processing. Scientists and businesses have been inspired to develop a more nutritious and environmentally friendly food supply chain by the growing awareness of good eating habits and dietary habits. Seeking to exploit the prospective use of cellulosic components as

an organic ingredient in food enhancers has mostly been driven by this desire. Additionally, cellulose is recognized as a crucial source of dietary fiber without calories that can enhance consumer's health [98].

Alzate-Arbeláez et al., 2019 suggested that a naturally derived additive made of nanocellulose using banana rachis and endogenous antioxidant from Andean berry (*Vaccinium meridionale*) may be employed. The efficient uptake of polyphenols from Andean berries has been made possible by the Physico-chemical characteristics of nanocellulose created by acid hydrolysis [99]. The combination showed good heat resistance and antioxidant properties, making it a potential replacement for synthetic oxidant inhibitors. According to Wang et al., 2018, cellulose nanofibers (CNF) get the potential to serve as a flavor enhancer for goods high in fiber but reduced in fat [100]. It was discovered that adding 2% CNF to the meat mixture improved the chemical and sensory qualities of the sausages produced. Andrade et al., 2014 claimed that because adding nanocellulose from the refuse of peach palm to mice's meal had no adverse effects, it might be utilized as a nutritional supplement. They discovered that after ingesting diets supplemented with CNC at concentrations of 7%, 14%, and 21%, mice's overall body weight rose by 9–10%. These results showed that adding CNC to the food was appropriate and reliable because all the mice were in good health [101].

The hydrophilicity of cellulose is just another outstanding characteristic that helps to retain the moisture content within the food products [41]. Salma Mohamad Yusop and Nor Fazelin, 2016 discovered that nanocellulose might be used as a useful component in marinating meat. Skinless chicken breast fillet was marinated in cellulose and nanocellulose from pomelo albedo at a concentration of 0.5% each. It was discovered that this mixture significantly boosted the ability of chicken breasts to moisture [102]. The cellulose substance has an encouraging quality as a moisture-retaining agent in the marinating of meat. It aids in enhancing and maintaining the meat's softness and succulence.

Sebayang & Sembiring, 2017 examined the use of CMC from palm oil midrib as a flavor enhancer in ice cream items in a different study. The majority of the participants preferred the smoothness, flavor, fragrance, and appearance of the ice cream that had 0.5% CMC added to it. As the dense population of CMC was seen to successfully extend the melting period of the ice cream, the CMC structure works in synergy with other components in ice cream to preserve the durability of ice cream items [103] (Table 2).

Table 2 Cellulose and cellulose composites used in food items

Application	Products	Types of cellulose nanocomposites	Technology	Major functions	References
Food packaging	Cellulose based film	Gelatin-chitosan and starch-chitosan	Film casting	• Good thermal stability • Food preservation	[60]
		Hydroxypropyl methyl cellulose and jute cellulose nanofibrils	Solution casting	• Increase the storage modulus and tensile properties • Reduce the moisture affinity • Highly promising in the area of packaging and transdermal drug delivery system	[61, 104]
		Metallic (Ag, CuO, and ZnO nanoparticles) and regenerated cellulose hybrid nanoparticles	Solution casting technique	• Strong antibacterial activity against *E. coli* and *L. monocytogenes*	[54]
		Multifunctional cellulose nanocrystal/poly (lactic acid) nanocomposite containing silver nanoparticles	Solvent evaporation and spray drying method	• Effective mechanical, water vapor, and thermal barrier properties • Significant antibacterial action against *S. aureus* and *E. coli*	[105]

(continued)

Table 2 (continued)

Application	Products	Types of cellulose nanocomposites	Technology	Major functions	References
		Surface-modified montmorillonite is used in cellulose nanocomposite foam	High shear homogenizer method	• Improved thermal, mechanical, and barrier qualities as well as expandable polystyrene foam trays for packaging dry food	[64]
		Hydrophobic acrylate monomer- and antimicrobial macro monomer based core–shell antibacterial latex	Semi-continuous emulsion copolymerization technique	• Antibacterial activity against *E. coli* • Treatment of the paper surface for use in food packaging	[62]
		ZnO loaded cellulose	Hydrothermal method	• Strong antimicrobial activity against *S. aureus* and *E. coli*	[66]
		Cellulose nanofibrils, nanoclay/polyethylene glycol/PLA	Solution mixing	• High thermomechanical properties • High oxygen barrier • High transparence and disintegration	[63, 106]
		Durian rind cellulose and polylactic acid (PLA) combined with butylated hydroxytoluene (BHT)	Brabender internal mixer followed by hot press machine	• Potential as antioxidant-active packaging	[71]

(continued)

Table 2 (continued)

Application	Products	Types of cellulose nanocomposites	Technology	Major functions	References
		Cellulose nanofiber and sugarcane bagasse	Partial dissolution	• High tensile strength (up to 140 MPa) • Food packaging application as protective film	[73]
		CNC from paper-mulberry (*Broussonetia Kazinoki Siebold*) bast pulp with agar	Solution casting	• High tensile strength • Significant water vapor permeability	[74]
		CMC from mulberry paper and glycerol	Etherification	• Improved the packing film's physical properties	[75]
		CMC from durian rind and rice starch		• Excellent mechanical characteristic	[85]
		Cellulose nanocrystals, essential oils, and carnauba wax nanoemulsion	Solution casting	• Excellent barrier properties against fungal growth, water vapor permeability, and ultraviolet and visible light	[77, 107]
		Cellulose and Polyhydroxyalkanoates (PHA)	solvent exchange-cum-casting		[68]
		Cellulose nanofibrils (CNF) from waste coconut husk and poly (vinyl alcohol) (PVA)	TEMPO mediated oxidation	• CNF acts as filler for PVA material in food packaging	[108]

(continued)

Table 2 (continued)

Application	Products	Types of cellulose nanocomposites	Technology	Major functions	References
		CNFs and nano-calcium carbonate (NCC)	Solution mixing	• Coat and protect a plant, fruit, and vegetable in food packaging	[109]
Food/drug delivery system	Microcapsules, CNC-based carriers	CNCs extracted from bacteria with methacrylamide	Acid hydrolysis	• Improve delivery system, and biological activity of substances • Decrease the side effects of functional food • Increase of the carboxylic groups on the CNC surface could retard the release of the loaded drug	[110]
		PVA/CNC hydrogel as the carrier of methylene blue dye	Photo crosslinking	• CNCs increased the dye adsorption capacity to 65%	[111]
Food supplements	Thickener	Carboxymethylcellulose (CMC)	Melt extrusion followed by a film formation process	• Syrup becomes thicker • Prevents fat from interacting with the digestive fluid	[103, 112]
		Bacterial cellulose (BC) in whey protein isolate (WPI) emulsion	Solution mixing	• Increase the gel strength of tofu • Prevent cocoa precipitation in a chocolate beverage	[86]
		CNC in chitosan/guar gum nanocomposite suspension	Solution mixing	• Create an entangled network, which increases viscosity	[56]

(continued)

Table 2 (continued)

Application	Products	Types of cellulose nanocomposites	Technology	Major functions	References
		CNF in milk	TEMPO mediated oxidation method	• Superior thickening behavior in milk	[113]
	Emulsifier	Cellulose microfibre in sunflower oil in water emulsion	High pressure homogenizer	• Stabilized 40/60 ratio of sunflower oil in water emulsion at concentration 0.75%	[114]
		(MFC) from mangosteen rind in 10% soybean oil-in-water emulsion	Solution mixing	• Have long-term storage stability for up to 80 days at concentration >0.50% of MFC	[90]
		Nanofibrillated cellulose (NFC) from mangosteen in mayonnaise	Solution mixing	• Increase the storage stability of mayonnaise up to 8 weeks	[91]
		Cellulose nanocrystal (CNC) from pistachio shells, cellulose fibre from banana, cellulose from sugar beet leaves in oil in water emulsion	Acid hydrolysis method	• Higher the concentration of CNC, the higher the stability of emulsions toward heating, stresses and period of storage • Reduce the interfacial tension, thus enhancing the emulsion's stability	[115]
		Bacterial cellulose (BC) in olive oil-in-water emulsion	Solution mixing	• 0.05 percent of BC can stabilize a 15 percent weight oil-in-water emulsion at pH 7 for four weeks	[95]

(continued)

Table 2 (continued)

Application	Products	Types of cellulose nanocomposites	Technology	Major functions	References
		Cellulose microfibers in sunflower oil	Solution mixing	• A low-calorie product that replaces trans and saturated fats in food with dietary fiber	[89]
	Anticaking agent	Microcrystalline cellulose (MCC) in shredded cheese	Mixing	• High flowability of the powder and little interparticle stickiness	[116]
	Calorie reducer	Cellulose microfibre in sunflower oil and water emulsion	Mechanical treatment through a high-pressure homogenizer	• Promising low-calorie product containing dietary fiber, replacing trans and saturated fats in foods to treat weight disorders	[89]
	Dietary fiber and functional foods	BC, dried foods and drugs (powdered) comprising nanocellulose and water-soluble saccharide	Mixing	• Prevent agglomeration of nanocellulose • Encourages favorable physiological consequences such as diarrhea, reduce blood cholesterol, intestinal problems, and reduce blood sugar	[117]

(continued)

Table 2 (continued)

Application	Products	Types of cellulose nanocomposites	Technology	Major functions	References
	Body weight increaser	Nanocellulose from peach palm waste into the diet of mice	Mixing	• After consuming diets enriched with CNC at concentrations of 7%, 14%, and 21%, mice's body weight increased by 9–10%	[101]
Food additives	Antioxidant	Nanocellulose from banana rachis mixed with Andean berry (*Vaccinium meridionale*)	Mixing	• Excellent antioxidant • Preservatives with heat resistance	[99]
	Fat reducing agent	CNF (2%) into meat batter	Mixing	• Fiber-rich food products with low-fat content	[100]
	Water binding agent	Skinless chicken breast marinated with nanocellulose from pomelo albedo	Marinated with 0.5% of cellulose and nanocellulose	• Increased the water-holding capacity of marinated chicken breasts	[118]
	Melting time prolonger	CMC from palm oil midrib in ice-cream	Agitation, pasteurization, homogenization, freezing	• Effectively prolong the melting time of the ice cream • Highest preference of texture, taste, aroma and color	[119]

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Regenerated Cellulose and Composites for Biomedical Applications

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Abstract The growing demand for bio-based materials is gaining traction in biomedical fields like tissue engineering and drug delivery (Khan et al. in Inorg. Chem. Commun. 134, 2021). Polysaccharides, which are long-chain biopolymeric carbohydrate molecules composed primarily of monosaccharide units, are bio-based materials that combine enormous potential in biomedical applications with the distinct advantages of natural polymers over synthetic polymers (Zamel and Khan in Polym. Adv. Technol. 32:4587–4597, 2021). Cellulose is one of the most common biopolymers on the planet, originating primarily from plants, wood, and bacteria. It is made up of randomly assembled, 100 nm wide ribbon-shaped fibrils that are made up

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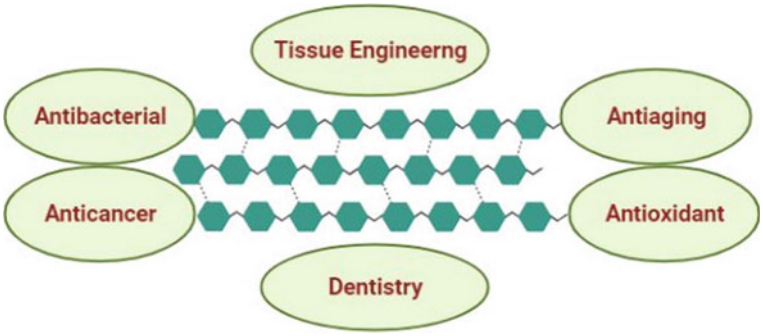
of 7–8 nm wide elementary nanofibrils aggregated in bundles (Gorgieva and Trček in Nanomaterials 9:1352, 2019). As such, it offers a unique combination of properties, including flexibility, high water holding capacity, hydrophilicity, crystallinity, moldability in various morphologies, elevated purity with no lignin or hemicellulose, and a biomimetic three-dimensional (3D) network. Because of these characteristics, this type of cellulose is gaining popularity for various medical applications (Seddiqi in Cellulose 28:1893–1931, 2021; Zamel in Sci. Rep. 9:1–11, 2019). Due to their suitable physical and mechanical properties, cellulose and its derivatives have attracted considerable attention as biocompatible polymers for applications in the biomedical field. Cellulose naturally develops functionality, flexibility, and high specific strength (Ansari in Compos. A Appl. Sci. Manuf. 74:60–68, 2015).

Graphical Abstract



1 Introduction

Cellulose-based materials has wide biomedical application such as use as drug carrier wound dressing and sanitary products in biomedical fields because of their low-cost abundance in storage and excellent renewability. As known, there is a bid demand on bio-based materials for the immediate biomedical applications, for instance, wound healing, tissue engineering, and drug delivery [1]. The long-chain macromolecules, such as polysaccharides, are mainly composed of monosaccharides' units which are bio-based materials which play a significant role in biomedical applications. Among these polysaccharides, cellulose can be considered the most common natural biopolymer based on its availability in wood and plants [2, 3]. Furthermore, cellulose is unbranched polymer which consists of repeated glucose units forming a long chain of an organic biodegradable polysaccharide [4]. Cellulose as a biocompatible polymer and its derivatives exhibited excellent characteristics in application in biomedical field based on their unique physical and chemical properties such as flexibility, functionality, suitable strength, and hierarchical structure [5]. In this

book chapter, we focus on the biomedical applications of cellulose and its derivatives such as antibacterial, anticancer, anti-aging, antioxidant, tissue engineering, and dentistry. Cellulosic materials have not efficient antibacterial activity because of easy to be infected by bacteria [6]. Therefore, to overcome the previously mentioned problems, developing efficient antibacterial cellulosic materials is highly required [7, 8]. Nowadays, commonly three methods are used to prepare cellulose-based materials having effective antibacterial activity, that are by adding natural antimicrobials [9] by incorporating metal ions [10] or nanoparticles [11] by introducing functional groups with antibacterial activity such as quaternary ammonium salt and Schiff base [12].

2 Antibacterial

Cellulose-based materials have wide biomedical application such as use as drug carrier wound dressing and sanitary products in biomedical fields because of their low-cost abundance in storage and excellent renewability [13–15], but generally cellulosic materials have not efficient antibacterial activity because of easy to be infected by bacteria [6]. Therefore, to overcome the previously mentioned problems, developing efficient antibacterial cellulosic materials is highly required [7, 8]. Nowadays, commonly three methods are used to prepare cellulose-based materials having effective antibacterial activity, that are by adding natural antimicrobials [9] by incorporating metal ions [10] or nanoparticles [11] by introducing functional groups with antibacterial activity such as quaternary ammonium salt and Schiff base [12]. Cellulose-based materials have wide biomedical applications, and different synthesis methods are used to prepare good antibacterial activity cellulose-based materials [16]. Currently, in a recent research, Schiff base methods are used to prepare cellulose-based materials. Cellulose fibers and copper ions were complexed with Schiff base to form complex. The synthesized complex has greatly improved the antibacterial properties of cellulose fibers. The characterization results confirmed the successful synthesis of Schiff base and its copper (II) complex after synthesis. The synthesized complex is checked for antibacterial activity of different bacterial strains, and the antibacterial test showed that the width of zone of inhibition of the synthesized cellulose-based Schiff base–Cu(II) complex increased 472 and 823% against E. coli and S. aureus as compared to Schiff base ligand. This improved activity is due to the incorporation of copper ions (II), and this Schiff base–Cu(II) complex contains cellulose-based materials which will be widely used for antibacterial activity in future research [17]. Similarly, in another research carboxymethyl cellulose/ZnO nanocomposites hydrogels are prepared by in situ formation of ZnO nanoparticles within swollen carboxymethyl cellulose hydrogels. For characterization X-ray diffraction scanning electron microscopy and UV–vis spectroscopy were used; these studies confirmed the formation of ZnO nanoparticles in the hydrogels. In hydrogel matrix, SEM micrograph showed the synthesis of the ZnO nanoparticles with size which are in range of 10–20 nm. The synthesized nanocomposites' hydrogels showed a

salt-sensitive and pH swelling behavior. In comparison with neat hydrogels, the ZnO nanocomposites' hydrogels have higher swelling in different aqueous solutions. Synthesized nanocomposites showed excellent antibacterial effects against S. aureus and E. coli bacteria, so this result showed that synthesized nanocomposites' hydrogels can be used for biomedical applications [18]. Similar work done in another research in which immobilization of silver nanoparticles on TiO_2 nanoparticles are performed; subsequently, TiO_2/AgNP are incorporated into cellulose acetate (CA) nanofiber matrix. Silver nanoparticles have excellent antimicrobials' effects, but high release of Ag causes argyria and argyrosis; so to prevent this defect, this research is done. In this method, first of all TiO_2/AgNP nanocomposites are synthesized by treatment of $AgNO_3$ solution with coated polydopamine hydrochloride TiO_2 nanoparticles. Afterward, synthesized nanocomposite was put into cellulose acetate (CA) solution and electrospun for fabrication to form cellulose acetate/titanium dioxide/silver nanoparticles' composite fiber. Afterward, the synthesized composite is analyzed by different characterization techniques such as transmission electron microscope, XPS, XRD SEM, FTIR, and EDX and antibacterial assays [19]. In another research, biodegradable composites filters are prepared through an in situ deposition method to inactivate bacterial and isolate pollutants from environment because these environmental issues such as toxic gases, microbial pollution, and particulate matter have serious effects on human health. In this research, silver-based metal–organic frameworks@CF are generated which displayed high antimicrobials' properties against *E. coli* which shows zone of inhibition 20.8 mm of diameter as well as these (Ag-MOFs@CF) composites' filters could be potentially used in alleviating environmental problems and also in different healthcare fields [20]. Ma, S., et al. have also reported (CA/CNT/AgNPs) nanofibers' composite for different antimicrobial uses. In this method, silver nanoparticles are fixed on carbon nanotubes and then embed composite inside cellulose acetate matrix to prevent harmful effect of silver (i.e., *argyria* and *argyrosis*). It is expected to show reduced silver leaching. By electrospinning of cellulose acetate nanofibers loaded with AgNPs, anchored multiwall carbon nanotubes (CNT/Ag) are prepared. CA/CNT/silver nanofibers' composites showed regular morphology which confirms through SEM analysis. Anchoring of AgNPs on carbon nanotubes and inserting carbon nanotube/silver in the cellulose acetate nanofibers' matrix are studied through TEM. Outstanding antibacterial results of the prepared nanocomposites are demonstrated through antibacterial test. On agar plate, the cellulose acetate/carbon nanotube/silver nanoparticles' composite showed outstanding bacterial growth inhibition, so it is confirmed that the synthesis of CA/CNT/Ag nanocomposites' nanofibers possesses good antibacterial characters against different bacteria [21]. Bacterial cellulose-based silver nanoparticles are developed for wound dressing and antimicrobial purpose and the synthesis done through UV light irradiation which is a green facile technique bacterial cellulose (BC) has porous three-dimensional webs like structure gained by ultraviolet light irradiation. After that, antibacterial activity is examined on the hybrid composites such as pellicles against Gram-negative bacteria *E. coli* through well-diffusion and growth dynamic methods which showed excellent bacterial killing performance, and after a long soaking time, no significant amount of silver release from the silver/bacterial

cellulose pellicles is observed. So, by combining all these properties, the composites' pellicles have also excellent applications in treatment of wound healings [22]. Similar work has also reported in another research using an environmentally safe and cost-effective method; hydrothermal synthesis was used; silver nanoparticles were synthesized by the help of BC as a reducing and stabilizing agent because cellulose material has excellent antibacterial applications; and to achieve good antibacterial activity of the bacterial cellulose/silver nanoparticles' composite, some key parameters are optimized, and under strictly optimized conditions, a narrow distribution of silver nanoparticle 17.1 ± 5.9 nm small size is formed on the bacterial cellulose matrix which has minimum inhibition concentration value of $1.30 \times 10{-}4$ μg/CFU and contains silver contents of 1.78% (w/w). Furthermore, antibacterial activity is performed, and constant release of Ag and persistent antibacterial performance confirm that synthesized composite material has excellent antibacterial properties against Staphylococcus aureus after along long period of 72 h. Exposure to composites' material proved that synthesized composite has strong antibacterial applications [23]. Likewise, non-solvent-induced phase separation and in situ deposition methods are used for the preparation of a multifunctional Ag@AgCl-cellulose acetate/silk fibroin composite films for the photocatalytic activity to decompose methyl orange (MO) and also employed as antibacterial against different bacterial strains. The CA/SF film is used because it is an eco-friendly substrate and providing site for Ag@AgCl nanoparticle in situ deposition and various analytical methods are used for the characterization of synthesized composite. Under visible light, the decomposition of methyl orange (MO) showed the photocatalytic activity of the films and the results clearly indicated higher photocatalytic activity of Ag@AgCl-CA/SF than silver-cellulose acetate/silk fibroin and showed 10.3 times photocatalytic activity of MO decomposition than Ag-CA/SF. After that, films are employed for *S. aureus* and *E. coli* bacterial strain and showed good activity, so the results declared that synthesized films well are exploited for bacterial inactivation and pollutant degradation [24]. Silver nanocluster-based hydrogel by using BC (AgNC@BC) is prepared by in situ formation method; the synthesized Ag nanocluster-based hydrogel showed excellent performance against both Gram-positive and Gram-negative bacteria and expresses long-acting bactericidal efficacy as compared as to pristine Ag NCs because of its controlled-release features for Ag species. Besides these important antibacterial properties, the fabricated hydrogel possesses good biocompatibility and has great applications in battling of various bacterial infections [25]. As bacterial infections are increasing day by day, sterically stabilized nanocrystalline cellulose (SNCC) are prepared functionalized with aldehyde groups to facilitate the attachment of antibacterial agents nisin and lysozyme, and immobilization is achieved by a simple, green process without activator or linker. The attachment of both nisin and lysozyme onto the SNCC is confirmed by XPS and FTIR. After that, synthesized conjugated nanocellulose is confirmed against the model bacteria *S. aureus* and Bacillus subtilis; the result clearly expressed that conjugated nanocellulose has higher minimum inhibitory concentration as compared with free form nisin and lysozyme, and it is also suggested that synthesized nanocellulose will be highly

efficient in the development of antibacterial wound dressing [26]. As bacterial cellulose has great application, chitosan (CS) and bacterial cellulose semi-interpenetrating network (semi-IPN) hydrogels are synthesized and cross-linked with glutaraldehyde. Various characterization techniques are applied including XRD, TGA, FTIR, FE-SEM, and rotational rheometry to characterize BC-CS hydrogels. The results clearly showed that BC was physically attached with network forming semi-IPN hydrogels and also indicate cross-linking of glutaraldehyde with chitosan chains and cross-sectional freeze-dried hydrogels indicate microporous openings which is confirmed through microscopic study. High mechanical properties of semi-IPN hydrogels are confirmed through rheological results, and BC-CS hydrogels showed higher thermal stability than pure BC film or CS hydrogel alone. After synthesis, the hydrogels are tested against Gram-positive and Gram-negative bacteria and it's confirmed that the antibacterial properties depend on BC to CS ratio, hydrogels with 20% BC to CS ratio inhibit 88% of viable colonies, and this development confirms that the synthesized BC-CS stable material is a promising candidate for antibacterial applications [27]. Useful and sustainable materials are synthesized for diagnostic and biomedical purpose. Bio-nanocomposite materials have excellent application in biomedical field; in recent research, cellulose/copper nanoparticles' bio-nanocomposites are synthesized utilizing bio-fluent as reductant of the precursor copper ion for in situ synthesis of copper nanoparticles in cellulose matrix. After that, it is confirmed that synthesized copper-based bio-nanocomposites at concentration of 250 mM of Cu showed excellent bacterial activity against *E. coli* with a zone of clearance of 12 mm and also possess excellent corrosion resistance [28]. Similarly, in another research, silver nanoparticles are prepared on cellulose nanofibers through thermal treatment method and use DMF as reducing agent. First of all, by using deacetylation of electrospun cellulose acetate (CA), cellulose (CE) nanofibers are prepared then by thermal silver coating through induced reduction process. Excellent antibacterial performance of the synthesized CE AgNPs is confirmed through antibacterial results against *E. coli* and *S. aureus*. So, on the bases of spatial distribution of AgNPs on cellulose nanofiber, excellent antibacterial performance confirms that the synthesized CE AgNPs are a good candidate for effective antimicrobials activities [29]. ZnO-bacterial cellulose-based material is generated for the first time and the nano-zinc-bacterial cellulose-based material is biocompatible and excellent antibacterial properties. The synthesized material was tested against *B. subtilis spizizenii Nakamura* (ATCC 6633), *Escherichia coli* (ATCC 8737), mammalian cells (human dermal fibroblast cells), and *Candida albicans* (ATCC10231) for antimicrobial properties. So, on the basis of these results, it is suggested that synthesized BC composite material is biocompatible and also has strong antibacterial properties [30]. Another facile approach was used for the synthesis of cellulose-based material to synthesize gelatin-based nanocomposite for different medical applications. The synthesized hybrid films showed excellent antibacterial activity against Gram-negative (E. *coli*) and Gram-positive (S. *aureus*) pathogenic bacteria due to fusion of silver nanoparticles in the gelatin matrix, and also it is confirmed that gelatin-based nanocomposite films are biodegradable and also exhibited strong thermal stability, water resistance, UV-shielding capacity, and antibacterial properties and the novel method are also

applicable as packaging materials [31]. Another green and facile approach is used for the synthesis of silver-carboxylated nanocellulose (Ag-ONCs) nanocomposites for different industrial and antibacterial applications. A simple method was used for the preparation of silver-ONCs; in this method, the treatment of ammonium persulfate (APS) with agriculture bagasse waste is performed. Due to presence of the specific hydroxyl and carboxyl groups on the cellulose surface, the ONCs act as a template and reducing agent for AgNPs' formation. The results displayed that quasi-spherical, well crystalline about 4–10 nm dispersed silver nanoparticles in the ONCs' matrix. Qualitative antibacterial test of the synthesized nanocomposite are performed using Gm +ve *S. aureus* and *Bacillus subtilis* and Gram-negative *E. coli* and Pseudomonas aeruginosa) and the results presented zone of inhibition for both groups of bacteria [32]. Furthermore, precipitation method is used for making efficient antibacterial material; in this method, cellulose/titanium dioxide nanocomposite is prepared using coagulation in sodium hydroxide–thiourea–urea aqueous solution. The synthesized nanocomposite is then screened against various bacterial species including *E. coli* and *S. aureus* and the material showed excellent antibacterial performance [33]. As cellulose has wide application in daily life but vulnerable to growth of microorganism, in a recent report, cellulose scaffold is incorporated with silver titanium dioxide nanoparticles to prepare efficient composite material against bacteria through a simple sol–gel technique. The results clearly displayed that the synthesized silver/titanium dioxide/cellulose composite films has strong antibacterial function against all samples due to the presence of silver contents and 0.030 wt% has strong ability of inhibition of more than 99% against *E. coli*. So, the study suggests that the synthesized nanoscale composite is effective against bacteria [34]. Using a facile chemical precipitation method, cellulose nanocrystal (CNC)-doped zinc oxide nanoparticles are prepared by using different concentrations of Mg for the degradation of methylene blue (MB) and also to use against bacteria [35]. Nowadays, biofilms are strong cause of different infections and also show resistance to different antibiotics which are a rising challenge in biomedical field; in a recent research, biocompatible composite is synthesized by combining tannic acid and MgCl2 to BC for antimicrobial purpose. In vitro release study of the synthesized composite displayed that the Mg^{2+} cross-link helps in block the discharge of TA from bacterial cellulose matrix while bacterial cellulose/tannic acid lacked Mg^{2+} ionic cross-links, so high amount of TA was discharged from the hydrogel. The synthesized composites also showed excellent antibacterial activity against *P. aeruginosa*, *S. aureus,* and *E. coli.* Therefore, the results confirm that the synthesized material is biocompatible and high combating anti-biofilm-associated infection material and has high application in biomedical field [36]. Bacterial cellulose has numerous applications, but it has lower antibacterial activity; so, to improve its antibacterial performance, GO and CuO are incorporated into bacterial cellulose to prepare BC/GO-CuO nanocomposites. The prepared nanocomposites displayed outstanding antibacterial performance against Gram-negative and Gram-positive bacteria as compared with BC/CuO alone. Besides this, the synthesized nanocomposites have high biocompatibility toward mice fibroblast cells [37]. Similarly, in another research, antibacterial nanocomposites are developed; in this method, nanosilica is obtained through modification

of cellulose fibers of lyocell by nanosilver particle. In this method, 50% of water solution chemical reduction of silver nitrate was performed, and then, N-methyl morphine N oxide is used as direct cellulose solvent for the generation of lyocell fibers. The results displayed that the synthesized fibers are safe for human tissue and suitable for medical purpose as well as the material has excellent antibacterial properties [38]. The RC films coated with Cu nanoparticles have efficient antibacterial properties; the regenerated cellulose (RC) films coated with CU nanoparticles are synthesized by the coagulation of cellulose–cuprammonium solution in aqueous sodium hydroxide and reduced by aqueous NaBH4. The synthesized material killed all bacteria within one hour and reduces viable bacteria when expose for 0.5 h [39]. Cellulose acetate has been obtained through hydrolysis of cellulose diacetate (CDA) having different degrees of substitution of 1.75∼2.17; also, cellulose acetate sorbate (CASA) is prepared through esterification of sorbic acid (SA) and cellulose acetate. Besides this, the synthesized cellulose acetate sorbate films synthesized through casting techniques have superb mechanical properties and have potential application in healthcare fields [40]. Similarly, in another research, cellulose acetate, poly (ε-caprolactone), and dextran blends' solution are used for synthesis of electrospun nanofibrous mat for antibacterial and wound dressing purpose. To improve blood clotting ability, cell attachment as well as antimicrobial performance, a small amount of antibacterial drug tetracycline hydrochloride was incorporated in composite mat. The results displayed strong proliferation of the cells and also enhanced adhesion on the composite fibers because of the incorporation of dextran and also showed strong zone of inhibition against Gram-negative and Gram-positive bacteria which indicate strong antibacterial activity of the composite fibers, and also, the synthesized composite fibers have skin engineering and wound dressing application [41]. Similarly, in a recent research, multiporous bacterial cellulose modified by N-isopropyl acrylamide (NIPAM) films is prepared and then tested for antibacterial properties after chlorination. The synthesized films showed excellent water retention and have high porous layered structure which can be further used for wound dressing. Furthermore, the chlorinated films have displayed good biocompatibility and hemostatic ability on wound bleeding. So, the results clearly demonstrate that N-halamine-functionalized MBC has greater applications in wound dressing and antibacterial activity [42]. In another research, cellulose/silver/silver chloride hybrids are prepared through ultrasound agitation method in which use cellulose, $AgNO_3$, and $AlCl_3$. $6H_2O$ to investigate properties and fabrication. The hybrids and results displayed good thermal stable cellulose/silver/silver chloride synthesis of the hybrid and showed excellent antimicrobial properties [43]. As a bacterial cellulose is an abundant source of carbon and carbon materials have wide application in waste water treatment and antibacterial properties, in a recent research, carbonized bacterial cellulose composite is synthesized using silver nanoparticles for antibacterial purpose using bacterial cellulose because bacteria cellulose is a rich source of carbon and also has wide applications. The synthesized composite is a strong candidate in water purification as well as has high antibacterial properties [44]. To prepare stable silver nanoparticles through a rapid and reliable process and possess efficient antibacterial properties using nanocellulose are also reported. Dialdehyde cellulose nanocrystal are used as

stabilizing and reducing agent to make stable silver nanoparticles. Using cellulose nanocrystals has greater ability to reduce silver ions and to get cellulose nanocrystals-AgNPs composite with high silver percentage. Spherical shape of silver nanoparticles has been confirmed through transmission electron microscope image in CNC-AgNPs composite which size varies from 30 nm to several nanometers. Also, the composites' material displayed good antibacterial performance against *S. aureus* and *E. coli,* and also, the synthesized composites have applications in food packaging materials [45]. As studied, the surface of cellulose nanofiber mats made through layer by layer self-assembly technique that is negatively charged pectin and positively charged lysozyme are alternately deposited. Besides this, results displayed that nanofibrous mats coated by 10.5 lysozyme/pectin bilayer-structured mats have strong inhibitory effects when the antibacterial test of LBL-structured mats and cellulose mats is performed upon *S. aureus* and *E. coli* [46]. Similarly, alternative research uses a simple and less expansive method by exploiting nano-zinc oxide for the fabrication of antibacterial cellulose fibers. The fabricated fibers have greater feasibility and longer duration utility without any damage and breakage indicated by the tensile stress–strain curves. Excellent antibacterial devastating properties are studied against *E. coli.* In addition, it is observed that by keeping all the parameters constant, variation of sodium alginates displayed excellent impacts on *Escherichia coli.* So, the results confirmed that synthesized nano-zinc oxide–sodium alginate cellulose has excellent antibacterial application and suitable for biomedical purpose [47]. Iron copper alloy-decorated cellulose nanocrystals are synthesized via simple reduction reaction, and the results have clearly indicated that the synthesized Fe–Cu@CNC composite has excellent antibacterial application and also is capable for removing heavy meatal from waste water [48]. In today's modern world, making environmentally friendly material is of major concern and using natural material is very safe and cost-effective; in a recent research, natural material is used for making antibacterial mats having great antibacterial activities. By using electrospinning technology, cellulose acetate is synthesized which is converted via alkali hydrolysis into cellulose mats. The synthesize mats are further tested for antibacterial activity, and the results displayed superb antibacterial activity on *E. coli* up to 99% and *S. Aureus* over 86% which confirmed that layer-by-layer cellulose composite has excellent mechanical properties and antibacterial activity and its further study confirmed that cellulose composite is also applicable in wound dressing and food packaging [49]. It was studied that bacterial cellulose has a lot of biomedical application due to robust mechanical properties, non-toxicity, and water holding capacity but lack of excellent antimicrobial properties; in a recent research, bio hybrid systems are synthesized using bacterial cellulose and metal phenolic network to develope efficient BC nanofibrillar network. Different plant-derived tannic acid and metal ions are also used for this highly bacterial cellulose nanofibrillar network to enhance antibacterial properties [50]. As seen, bacterial cellulose has excellent mechanical and physical properties and is useful in numerous applications. It is also applicable in wound dressing but lacks efficient antibacterial performance; in a recent research, it is reported to synthesize efficient bacterial cellulose composite to enhance its antibacterial activity, so for this purpose bacterial cellulose is incorporated with sodium alginate, copper sulfate, and chitosan to

enhance its antimicrobial activity. The synthesized bacterial cellulose/sodium alginate/copper sulfate/chitosan composites are systematically studied to determine the structures and properties. The most observed properties comprise swelling ratio, tensile strength weight fraction, and release characteristics of copper. The synthesized composites displayed excellent antibacterial activities against Gram-negative bacteria E. coli and Gram-positive (MRSA). So, the results displayed that prepared composites are safe and have excellent applications as antibacterial and also safe and applicable for antimicrobials wound dressing [51].

3 Anticancer

Cancer is one of the leading causes of deaths worldwide due to lack of efficient treatment. Cancer is uncontrolled cell division which leads to tumor cells' proliferation; various anticancer treatments [52] are applied but all in vain because anticancer treatment may often result side effects; besides this, chemotherapeutics agents are also applied, but low availability, weak water solubility, and inefficiency are the major challenges for efficient performance against cancer treatment [53–55]. Nowadays, the materials based on cellulose have various applications as well as they have unique anticancer properties as demonstrated in a recent research. Curcumin–cyclodextrin/cellulose, nanocrystalline complexes have been synthesized for cancer treatment. Furthermore, to encapsulate curcumin, cellulose nanocrystals are functionalized by using ionic association with cationic b-cyclodextrin and cyclodextrin/ cellulose nanocrystals. In vitro analysis of the prepared curcumin–CD/CNCx complexes is performed which displayed that synthesized complexes have higher anti-proliferative effects on prostate cancer cell lines and colorectal cancer cell lines which have lower IC50s than curcumin alone [53]. Besides this, in another research for supply of siRNA in cancer cells, surface-modified cellulose nanocrystals are prepared. Sequential process of hydrothermal desulfation and chemical modification are used to prepare cationic cellulose nanocrystals; after that, using two-step method of rolling circle transcription and magnesium chelation is complexed with modified cellulose nanocrystals by electrostatic interaction to obtain polymeric siRNA. The efficiency of the synthesized nanocomplex is optimized for efficient drug loading and releasing in the cytoplasmic environment. The synthesized nanocomplex displayed good gene knockdown efficacy, enzymatic stability as well as the synthesized complex possesses efficient platform for carrying anticancer drug delivery [56]. Similarly, in another research, carboxymethyl cellulose drug matrix hydrogels are prepared to deliver anticancer drugs. By solution casting method, carboxymethyl cellulose-based drug matrix hydrogel was synthesized by using amount of citric acid as cross-linking agent. The results concluded that synthesized bio-based material is a potential and controlled non-ionic drug delivery system for carrying anticancer drugs [57]. Moreover, in another research work, quercetin-loaded nanohybrid hydrogel is prepared which is very biocompatible and has both anticancer and antibacterial properties. In last, the QE/OPD-loaded nanohybrid hydrogels are tested against human

skin carcinoma cell line A431 and normal L929 murine fibroblast cell which indicated that synthesized nanohybrid possesses anticancer properties and biocompatible and also QE/OPD-loaded nanohybrid possesses antibacterial properties which impede the growth of *S. aureus* and *Trichophyton rubrum* strains [58]. Similarly, in another research by in situ carboxymethyl cellulose embedded by zinc oxide nanoparticles, bio-nanocomposites are synthesized and loaded with hydrophobic anticancer drug curcumin (Cur). The results demonstrated that the synthesized nano-matrix has the ability to deliver anticancer drug curcumin and suitable for anticancer therapy [59]. As we have described cellulose have excellent biomedical applications, similarly cellulose nanocrystals loaded with 5-flourouracil, an anticancer drug, to determine its anticancer properties against colorectal cancer cells. The results proved that the synthesized CNC/5-FU is useful for colorectal cancer treatment and suitable for improved drug delivery [60]. The g-C3N4/MoS2 nanosheet and core–shell nanofibers are synthesized in which folic acid and doxorubicin are doped by using chitosan/ethyl cellulose core–shell nanofiber for delivering anticancer drug and folic acid. The maximum percentage of EC/chitosan/g-C_3N_4/MoS_2/DOX/FA nanofibers is found to be 85 and 89% against Hela and MCF-7 cells' death after seven days [61]. Furthermore, another tumor targeting drug delivery system is developed by layer-by-layer method based on electrostatic interaction to synthesize multi-layered targeting ligand chemotherapeutics–cellulose nanocrystals' structure. First of all, cationic doxorubicin (anticancer therapeutic agent) molecule is covered by negatively charged cellulose nanocrystals for fabrication of DOX@CNC, and after that, anionic hyaluronic acid is used to wrap the synthesized composite sequentially and successfully rod shape HA- coated DOX@CNC (HA@DOX@CNC). So, overall results confirmed that prepared HA@DOX@CNC tumor-targeted nano-sized drug delivery system is biocompatible and possesses outstanding drug delivery properties [62]. Similarly, by electrospinning techniques, a novel drug delivery system has been designed by using cellulose acetate and cellulose acetate/polyethylene glycol comprising 5-chloro-8-hydroxyquinolone as a model drug. The synthesized material (CA/5-Cl8Q and CA, PEG/5-Cl8Q) showed low toxicity and best anticancer activity; furthermore, the synthesized material also exhibited antifungal and antibacterial activities against *S. aureus, E. coli,* and *C. albicans.* So, the results also suggested that the synthesized material is suitable for local cancer treatment and wound dressing [63]. Furthermore, cellulosic walnut shell material using copper nanoparticles to evaluate its anticancer, antioxidant, and antibacterial performance is synthesized, and first of all, various sized CuNPs supported walnut shell are prepared such as CuNP-WS1 15–22 nm, CuNP-WS2 60–80 nm, CuNP-WS3 aggregated of metallic nanoparticles; then, antibacterial activity of copper nanoparticles is examined against three strains of bacteria including *E. coli, Listeria monocytogenes,* and *S. aureus,* and antioxidant activity is tested by using 1, 1-diphenyl-2-picrylhydrazyl (DPPH) process. Furthermore, cytotoxicity of the nanoparticles is examined against cancer cell line and showed dose-dependent cytotoxic effect on K562 cells and the IC50 which are observed (25.24 ± 5 μg/mL) against K562 cancer cells; also, the synthesized nanomaterial showed excellent antimicrobial properties and excellent antioxidant activity of copper nanoparticles when the concentration has increased

to 10% [64]. As described, a number of cellulose made drug delivery systems are designed for cancer treatment similarly in a recent research using layer-by-layer method to synthesize bio-nanocomposites by using chitosan and rice straw cellulose and using ionic gelation method for encapsulation of 5-fluorouracil (CS-CF/5-FU BNCs) and sodium tripolyphosphate as cross-linker and successful synthesis of CS-CF/5-FU BNCs. Furthermore, the synthesized bio-nanocomposites eliminated $56.42 \pm 0.41\%$ HCT-116 cancer cells at a concentration of 250 μg/mL and eliminated $8.16 \pm 2.11\%$ of CCD 112 normal cells, so the study showed that CS-CF/5-FU BNCs are a potential nanodrug carrier system for colorectal cancer treatment and chitosan nanoparticles, cellulose fibers, and bio-nanocomposites are biocompatible [65]. Another research also confirmed that cellulose-based carrier is good drug delivery system and delivers drugs to the target site accurately; similarly fabrication of BA-loaded cellulose-graft-poly (L-lactic acid) nanoparticles are reported which are comprised of betulinic acid (model drug), cellulose and poly (L-lactic acid) as material. Uniform size of 100–170 nm and spherical shape of BA-loaded and both drug-free are studied. Furthermore, in vitro cytotoxicity is performed which showed that CE-g-PLLA/BA nanoparticles have superior antitumor activity and have no toxic effects; the cytotoxicity is performed with A549 and LLC cell lines and the study strongly supported that the synthesized system is efficient for anticancer therapy [66]. As studied, cellulose nanocrystal has numerous biomedical applications; similarly, in a recent research, cellulose nanocrystals' surface is modified through direct anionic polymerization to prepare hyper branched polymers-functionalized cellulose nanocrystals using glycidol as monomer and surface hydroxyl group as initiators. Furthermore, functionalized CNCs peripheral end functional groups are transformed to hydrazide groups which could be used for loading anticancer drugs (epirubicin (EPI)). The functionalized surface nanocrystals are studied through HNMR spectra, FTIR, and TEM which confirmed that the synthesized cellulose nanocrystals are suitable for delivering anticancer drug [67]. Similarly, another cellulose-based hydrogel nanocomposites' films drug delivery system was designed for delivering anticancer drug doxorubicin having broad-spectrum anticancer properties. The novel nanocomposites are synthesized by using graphene quantum dots as nanoparticles and incorporated into carboxymethyl cellulose, and then, doxorubicin was used as model drug model which possesses excellent anticancer properties. MTT assays are used to study the DOX-loaded CMC/GQD nanocomposite hydrogel films against blood cancer cells, and at two different pHs, the drug release studies are carried out, and furthermore, SEM, FTIR, UV–vis spectroscopies were used to characterize the synthesized nanocomposite hydrogel. The synthesized CMC/GQD nanocomposites' hydrogel displayed excellent water vapor permeability, degradation, and in vitro swelling, and prepared nanocomposites are suitable for delivering anticancer drugs [68]. As effective cellulose-based nanomaterials are generated for efficient delivering of cancer drugs similarly oxidized cellulose, 2.3-dicarboxycellulose materials are synthesized for biological applications; the synthesized material which are conjugate of cisplatin and DCC possesses high drug lading and binding efficiency (>90%) and has excellent aqueous solubility; and in vitro study reveals that cisplatin-DCC conjugates lower toxicity toward healthy cells and possess excellent burst release of anticancer drugs

and more effective against prostate cancer, and also, in vitro study showed longer survival of conjugates and found more reduction in tumor volume [69]. Another efficient cellulose-based materials are generated for carrying anticancer drugs which are novel and simple and also cost effective, and for the first time, synthesis of this material is reported in which the surface functionalization and drug loading of CNCs by the synthesis of hydrazine bond between functionalized cellulose nanocrystals and aldehyde group comprising polyethylene glycol/anticancer drug (DOX) are prepared, and with pH-dependent manner, releasing of drug from complex (P-CNCs-D) and loading DOX in PEGylated cellulose nanocrystals with high capacity are observed, and this results displayed that drug carrier system could easily transport doxorubicin which possess excellent anticancer properties and also the drug carrier system has no negative cytotoxicity; this work opens a new avenue for fabrication and explores their biological applications [70]. As nanoparticles have numerous biological applications in a recent research through combination of carboxymethyl cellulose, starch, and zinc oxide nanoparticles, nanocomposite hydrogels' beads are synthesized for anticancer purposes and physical cross-linking is performed with iron chloride. The synthesized nanocomposite hydrogel beads are applied as efficient releasing of doxorubicin anticancer drug in the target site. Various methods are used including TGA, SEM, EDX, UV–vis, XRD, FTIR, and DSC for characterization of the synthesized nanocomposite hydrogel beads. Further, swelling and deswelling properties, gel contents, and drug release performance of the sample are also observed, and cytotoxicity is studied against human colon cancer cells (SW 480), and the drug release study confirms more controlled, prolonged drug releases and also showed that drug release performance depends on the concentration of zinc oxide nanoparticles contents [71]. Another study, novel drug nanocarriers are designed by using rice straw cellulose and Fe_3O_4 nanoparticles for carrying 5-fluorouracil (MC/5-FU) anticancer drug for treatment of colorectal cancer, and various properties of MC/5-FU bio-nanocomposites are observed through several analyses; furthermore, it is confirmed that Fe_3O_4 nanofillers covered the cellulose matrix by using scanning and transmission electron microscopy, and under various temperature and pH conditions, the drug release from MC/5-FU is studied which showed that at temperature 44.2 °C and pH 7.4, maximum release is observed. Moreover, MC/5-FU displayed excellent anticancer action and enhanced selectivity which confirms through in vitro anticancer assays when examined against 3D tumor spheroid models colorectal cancer cells and 2D monolayer, and the results further confirmed that synthesized nanocomposites have tremendous performance excellent formulation drug delivering system for colorectal cancer treatment [72]. Similarly, in another research, cellulose–magnesium oxide nanocomposites are synthesized which have excellent anticancer activity. Furthermore, nine experiments are designed by Taguchi method in which different stirring times and different ratios of magnesium oxide nanoparticles, cellulose biopolymers are chosen and successful synthesis of cellulose–magnesium oxide nanocomposites are confirmed by scanning electron microscopy. Furthermore, through MTT assay, the anticancer activity of nine nanocomposites is observed on MCF cell line which confirmed that experiment 9 which consists of 8 mg/ml magnesium oxide and 2 mg/ml of cellulose and

stirring time of 60 min has excellent growth inhibitory performance against studied cancer cells, which demonstrated that the synthesized nanocomposites are excellent anticancer agent [73]. Likewise, in another research using solvent exchange method with different molar ratios of cellulosic substrates, two composites poly (amidoamine) (PAMAM) hyperbranched polymer are synthesized for cancer treatment and the resultant composite synthesized by using TEMPO-oxidized cellulose and ethyl cellulose assigned COMP T and COMP E. Characterization FTIR and measurement of overall zeta charge are applied, and through SEM, the topography of composites is examined; furthermore, anticancer activity and cytotoxicity are also investigated; also through cell viability assays, the IC_{50} values are investigated by testing different types of composites and starting materials against MCF-7, WI-38, HCT-116, and HepG-2; and through inverted microscope, the morphological changes of cancer cell line are studied and excellent performance of the polyamidoamine is confirmed against carcinoma cell lines and low toxicity against normal cell lines observed. Furthermore, after combination of two types of cellulose with PAMAM, increased liver antitumor activity is studied; then, breast and colon carcinoma and also biocompatibility are observed against control cell lines [74]. Similarly, cellulose nanowhiskers/Pd complex is synthesized as prodrug anticancer system for delivering anticancer drugs, the cellulose nanowhiskers/Pd is prepared by acid hydrolysis of cellulose linter process which further used palladium (II) complex as a matrix, and different analytical process are used to characterize the prepared nanocomposite which includes SEM, FTIR, and UV–Vis. Due to the self-assembly of the cellulose nanocrystals showed fibrillary, network—like morphology which was confirmed by SEM images, and the synthesized nanocomposites showed enhance thermal stability than pure CNW. Furthermore, results confirm that synthesized nanocomposites are efficient drug delivery system for cancer [75]. Plant fruit shells (*Limonia acidissima*) (L) derived cellulose and magnetite nanoparticles; nanocomposites are successfully prepared through a cost-effective co-precipitation method. Furthermore, for successful synthesis of cellulose–magnetite nanocomposite, fructose and DES embracing choline chloride are exploited in non-toxic dispersant. Different analyzing techniques are used for characterization which includes X-ray diffraction, Fourier transform infrared spectroscopy, SAED, HRTEM, and VSM techniques to determine physiochemical parameters such as magnetic, compositional, structural, and morphological properties. Moreover, MTT and LRP assays are used to determine antitubercular and anticancer activities which showed that cellulose, magnetite, and cellulose–magnetite nanocomposites have IC_{50} values of 44.66, 20.65, and 8.685 μg/ml and also expressed excellent antibacterial inhibition against *M. tuberculosis*. So, the results confirmed that the synthesized nanocomposites are an excellent drug delivering system for cancer, and also the method is greener which is more safe [76]. As it was already described, various curcumin-loaded drug delivering systems for cancer therapy similarly in a recent research report successfully synthesis of gelatin microparticles through spraying drying method and loaded by curcumin, and furthermore, dialdehyde carboxymethyl cellulose is used as cross-linking agent to study in comparison with traditional cross-linking agents. Different parameters are used to successfully develop efficient drug delivery system and the

efficiency is determined through Taguchi method on gastric cancer, and the results displayed that synthesized system is more biocompatible drug delivery system and gelatin microparticles are cross-linked with DCMC. Various sizes of microparticles are prepared ranging from 1.926 to 3.357 μm at different parameters and curcumin showed stability for six months, and the results conclude that the synthesize DCMC cross-linked gelatin microparticle is an effective drug delivering system and has valuable biomedical applications [77]. Similarly, another drug delivery cellulose-based system was designed for anticancer purpose. First of all, oxidation of cellulose was performed with 2, 2, 6, 6,-tetramethyelpiperidine-1-oxyl radicle (TEMPO) and sodium periodate followed by sonication to prepare oxidized cellulose nanoparticles. After that on the synthesized oxidized cellulose nanoparticle, a model anticancer drug doxorubicin is loaded, and at different pH values, its release behavior is examined; in tumor tissue at pH 5.0 and pH 6.8, i.e., endosomal and extracellular pH, the anticancer drug doxorubicin releasing was maximum. Non-Fickian diffusion mechanism and different mathematical models are used to reveal the releasing mechanism of doxorubicin from loaded oxidized cellulose nanoparticles, and finally, the results conclude that synthesized drug delivery system is capable for carrying cancer treatment drugs and has no side effects on normal cells [78]. Another plant phytosterol, folate, and cellulose-based nanoparticles are prepared for delivering hydrophobic anticancer drugs first of all water soluble. Carboxymethyl cellulose and plant hydrophobic phytosterol are grafted and to prepare self-assembled FPCMCNPs the grafted material coupled by using folate as tumor targeting ligands, and furthermore, physiochemical properties of delivering system are described. After this with satisfactory loading content (7%) and loading efficiency of 71.2%, anticancer drug doxorubicin is entrapped on synthesized folate phytosterol carboxymethyl cellulose nanoparticles. Furthermore, in vitro drug release study was performed which revealed that at pH 5.3 the release amount of doxorubicin was high as compared with pH6.5 and pH 7.6. At final study, the results demonstrated that synthesized drug delivering system is efficient delivering system of anticancer drugs, but further experimental study needs to clarify its more functions [79]. Another novel biopolymeric nanocomposite hydrogel is synthesized through deposition of silver nanowires which are chemically cross-linked with carboxymethyl cellulose for delivering anticancer drugs first of all by grafting of poly [2-(methacryloyloxy ethyl trimethylammonium chloride] on carboxymethyl cellulose exploiting diethylene glycol dimethacrylate as cross-linker to synthesize the cross-linked polymer. and further, more nanocomposites are analyzed through various analytical techniques which include nuclear magnetic resonance spectroscopy/Fourier transform infrared spectroscopy, TGA, XPS, UV–vis, FE-SEM, and XRD analysis, and besides this, rheological analysis is used to determine the gel strength of the synthesized composite material. Furthermore, the curcumin-loaded composites are tested for anticancer activity which displayed the prepared composite kill the MG 63 cancers cell efficiently which proved that synthesized composites are efficient anticancer drug delivering system [80]. Another curcumin-loaded bacterial cellulose films are prepared by using curcumin solution at concentration of 0.5 and 1.0 mg/ml and analyzed through FTIR which

showed interaction between curcumin and bacterial cellulose microfibrils. Furthermore, antifungal activity of the synthesized material was tested against *Aspergillus niger* which displayed efficient antifungal activity. Moreover, high anticancer activity of the curcumin-loaded bacterial cellulose is found against malignant melanoma cells A375 and the efficient releasing of curcumin is achieved at pH 5.5 and 7.4 in target cells, and no significant toxicity of developed nanocarriers' system is found [81]. Similarly, another cellulose-based anticancer drug carrier system is designed by using alkali treatment method to isolate cellulose fibers from rice straw waste, and the derived cellulose fibers are used for carrying anticancer drug 5-fluorouracil (5-FU). Furthermore, properties of both pure cellulose and 5-fluorouracil drug as well as 5-fluouracil loaded cellulose fiber (CF/5-FU) sample are determined. Moreover, in vitro cytotoxicity of samples has been evaluated for 72 h treatment against normal cell line and human colorectal cancer, human nasopharyngeal cancer, and normal NP460 cell line. So from this, the results concluded that the designed system is efficient for delivering drugs against cancer [82]. As studied, numerous applications of magnetic nanoparticles recently magnetic nanocarriers are designed by using tris(2-aminoethyl) amine functionalized nanocrystalline cellulose (AMFC) decorated by iron oxide nanoparticles. Furthermore, MTX is loaded in design AMFC@MNPs and MTT assay and DAPI staining are applied which displayed that MTX-loaded nanocarriers have excellent cytotoxicity against MCF-7 breast cancer cell line when incubated for 48 h. So, the results confirmed that the synthesized system is efficient carrier to deliver MTX to the cancer cells [83]. Similarly, another drug delivery system is designed for carrying anticancer drugs to the target site; the novel drug delivery system is designed by using cellulose-grafted poly methacrylic acid–succinyl cyclodextrin for efficient releasing of 5-fluorouracil anticancer drug which is further grafted by Aminated–glcidylmethacrylate. Also, the cytotoxicity analysis confirmed excellent releasing of drug to the target site when tested on human breast carcinoma (MCF-7) which displayed that the synthesized system is efficient delivery system for delivering of 5-flouracil anticancer drug to the target site [84]. Using green source for formation of nanomaterial has great advantages; similarly, in a recent research, microgreen alga *chlorella vulgaris* is used for synthesis of nanocellulose, nanogold, and aurum/cellulose nanocomposites which have enhance anticancer properties; further, the synthesized nanocomposites are characterized by different analytical techniques which include FTIR, UV–Vis, TEM, absorption spectroscopy, and zeta potential analyzer which conformed the formation of synthesized nanoparticles. Besides this, selectivity and anticancer activity of the synthesized materials are examined against A549 cell (human alveolar basal epithelial cell). The cytotoxicity study expressed the inhibitory concentration of Au/cellulose nanocomposite 4.67 ± 0.17 μg/μL against A549 cancer lung cell and HEL 299 normal fibroblast cell which is 182.75 ± 6.45 μg/μL [85]. As cellulose derivatives have numerous applications in both commercial as well as in biomedicine field. Aminated cellulose has extensive application; similarly, in a recent study, 6-deoxy aminocellulose derivatives are synthesized from microcrystalline cellulose by tosylation. Furthermore, cytotoxicity of the synthesized materials has been determined against

breast cancer, melanoma cancer, and normal fibroblast cell. A number of cellulose derivatives are synthesized which include 6-deoxy-6-dietylamide cellulose (cell DEA), 6-deoxy-6-hydrazide cellulose (cell Hyd), and 6-deoxy-6-diethyltriamine cellulose (cell DETA) and numerous analytical techniques are applied for characterization of prepared cellulose derivatives which include SEM, NMR, FTIR-ATR, XRD, and elemental analysis and zeta potential measurement. After this, cytotoxicity of the prepared derivatives is determined against different normal and cancer cells which include mouse skin melanoma (B16F10), normal fibroblast (NIH3T3), and human (MCF-7) cell lines, and IC_{50} values analysis showed that MCC is non-cytotoxic, and cell Hyd, cell DEA, and cell DETA have no cytotoxicity up to 200 μg/mL to normal fibroblast cells and the most sensitive cell to cytotoxic effect is mouse skin melanoma (B16F10) to cell Hyd, cell DEA, and cell DETA after that MCF-7 (human breast adenocarcinoma is also sensitive to these depravities. So, on the bases of designed study, it is conformed that the synthesized aminated cellulose derivatives are suitable material for tissue engineering as well for cancer applications [86]. As we have already mentioned the potential applications of magnetic nanoparticles in biomedical field, similarly in a recent research, another nanosystem is designed for delivering of anticancer drugs to the target site; for this purpose, iron oxide nanoparticles are used to modify protamine and carboxymethyl cellulose polyelectrolyte multi-layered nanocapsule for transfer of anticancer drug doxorubicin against HeLa cells. High cellular uptake and enhanced drug intensity profile are examined when doxorubicin-loaded magnetic nanocapsules are applied in presence of magnetic field, so the final results confirmed that synthesized magnetic nanocapsules have valuable applications in carrying of anticancer drugs [87]. Various cellulose nanocrystals are developed for various applications as because of high biocompatibility and stability; in recent research, silver nanoparticles are generated through a minimized process and less use of chemical regents on carboxylate nanocrystal cellulose (cCNC). Furthermore, the synthesized silver nanoparticles' cellulose nanocrystals are tested for anticancer activity against human skin melanoma cells and human colon cancer cells and found efficient anticancer activity against these cell lines, and the maximum 15% activity is displayed against human skin melanoma cell and 18% against human skin melanoma cells, and cell viability are found for both are 35 ± 4.04% and 20 ± 7.68%. Also, it is confirmed from analysis that AgNPs have uniform deposition on cellulose nanocrystals and particle has maximum 15 nm size [88]. As natural polymers have less toxic effect and also cost-effective, in a recent research, bacterial nanocellulose films are created comprised different concentrations of mangosteen (*Garcinia mangostana).* The prepared nanocellulose films showed maximum bacterial inhibitory activity against different bacterial species due to composed of high phenolic compound as well as excellent anticancer performance which are investigated against MCF-7 breast cancer cells and melanoma $C_{16}F_{10}$ cancer cells having viabilities of 5 and 10% when treated for 48 h and low toxicity is found against normal keratinocyte cells and fibroblast cells [89]. Nowadays, demand of polymeric nanoparticles is very high because of their excellent biocompatibility and control drug release; similarly, now an efficient drug release process is designed for delivering anticancer drugs; in this method carboxymethyl cellulose-based pH

and redox dual- responsive polymeric nanoparticle, carboxymethyl cellulose–dithiopropionate hydrazide-8arm-polyethylene glycol-pterostilbene/10-hydroxyl camptothecin (CTPP/HCPT) are synthesized and the designed materials are well-dispersed and around dimension of 144 nm and displayed high biocompatibility and excellent binary drug loading capacity and synthesized materials have excellent advantage because of their fast releasing of drug payload and have sufficient stability. Besides this, in vitro and in vivo investigation confirmed excellent killing of cancer cells as well high suppressing capability of tumor growth of CTPP/HCPT NPs and also exhibit low adverse effects. So, the final results confirmed that the synthesized materials are suitable for cancer therapy [90]. Cellulose amphiphilic hydroxypropyl cellulose-based polymer comprised polyethylene glycol and cholesterol cancer-targeted drug delivery system is designed and the prepared system arise slightly modified by biotin conjugate (HPC-PEG-Chol-biotin); to effectively target cancer cells via dialysis method, the biotin conjugate is exploited to synthesize micelles, and in aqueous solution, a lower critical solution temperature of 39.8 °C is presented by polymeric micelles. Furthermore, spherical shape with 84 nm mean dimeters is observed through TEM and DLS analysis and the dimeters increases when temperature above LCST is increased. Further, the synthesized PTX-loaded HPC-PEG-Chol-biotin has strong adsorption and cellular uptake against MDA-MB-231 and HeLa cancer cells, and the MTT assays also confirmed strong potential and safe applications in tumor targeting [91].

4 Biosensors

A biosensor is a device that converts (bio) chemical information into an electrical signal using an appropriate transducer with a specific molecular recognition structure. As a result, a biosensor can be defined as an integrated receptor–transducer device that introduces precise and selective quantitative or semi-quantitative analytical data via a biologically active component [92]. Sensors and biosensors are critical analytical tools for the rapid, accurate, and early diagnosis of human diseases [93]. Biosensors are commonly used to detect biomolecules such as blood glucose, cholesterol, and genes. As the most prevalent natural polymer, cellulose has piqued the curiosity of many, particularly in the realm of medicine, such as advanced medical diagnosis. Cellulose could increase biocompatibility, biodegradability, and non-toxicity in biosensors, which could aid in medical diagnostics [94]. Composite materials based on a cellulose acetate matrix and several types of functional fillers were created for biosensors and bioanalysis applications. Yu et al., for example, developed a novel optical fiber biosensor for glucose detection by covering the end face of a 600 μm optical fiber with a sensitive film made of carbon quantum dots (CQDs) and glucose oxidase (GOD) distributed in cellulose acetate. The enzyme-based, fluorescent fiber-optic biosensor has a fast fluorescence response to glucose, as well as strong selectivity, repeatability, and anti-interference ability, allowing continuous real-time glucose detection even at low concentrations [95]. Multi-walled carbon nanotubes

(MWCNTs) were also mixed into cellulose acetate. The resulting aqueous dispersion was dropped onto a glassy carbon (GC) electrode to create a sensing probe for the electrochemical detection of key catecholamines like dopamine and epinephrine. The carbonaceous fibers had a random orientation and formed interconnected structures with the organic matrix, according to scanning electron microscopy (SEM) pictures [96]. Cellulose acetate worked as a perm-selective barrier, limiting catalyst poisoning and, therefore, boosting analytical performance and improving the mechanical stability and adhesion of the MWCNTs at the surface of the GC electrode. For the analytical detection of dopamine and epinephrine in pharmaceutical vials and human urine, the GC/MWCNT/CA biosensor was effectively used in procedures such as differential pulse voltammetry (DPV) and solid-phase extraction combined with liquid chromatography (SPE-LC) [97]. A simple hydrothermal treatment revealed carboxymethyl cellulose CMC to be an excellent material for manufacturing high fluorescence carbon dots. Sarkar et al. created a multifunctional system based on carbon dots decorated CMC and hydroxyapatite, which showed promising results in bioimaging. The carbon dots had a bright blue fluorescence emission of about 440 nm that was significantly suppressed in the presence of Fe^{3+} ions, indicating that ferric ions had a higher sensitivity than other metal ions [98]. Due to its commercial use, glucose biosensors have been one of the most investigated sensors. Because of its biocompatibility, low immunogenicity, biodegradability, and low cost, cellulose has been widely used to develop glucose biosensors [99]. Kim et al. created a low-cost, flexible, and disposable glucose biosensor by immobilizing GOx onto a cellulose–tin oxide (SnO_2) hybrid nanocomposite. The biosensor was made using a simple adsorption process of GOx onto cellulose paper and demonstrated strong storage stability, enhanced detection limit, good linear range, and high repeatability [100].

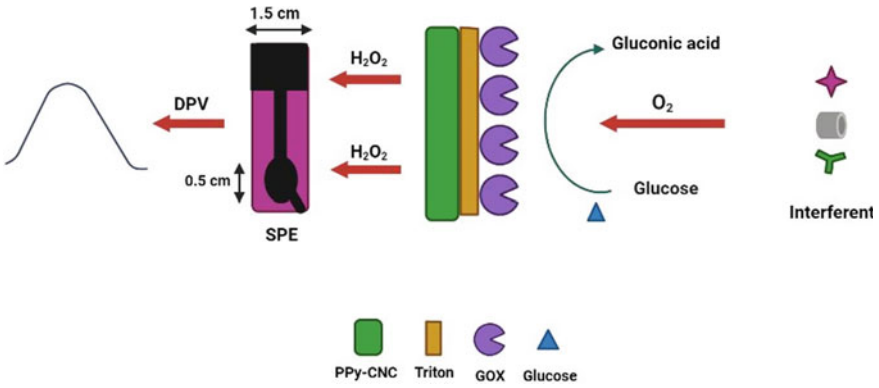


Fig. 1 Schematic illustration of electrochemical glucose biosensor based on PPy/CNC as a membrane [101]

As shown in Fig. 1, biomolecules can easily be entrapped while preserving their bioactivities in gold nanoparticle (Au)–bacteria cellulose (BC) nanofiber (Au–BC) nanocomposites due to their great biocompatibility, strong conductivity, and nanofiber network structure. Horseradish peroxidase (HRP) was employed as a model enzyme to immobilize on the Au–BC biocomposite in order to create a new H_2O_2 biosensor. When activated by hydrogen peroxide or other peroxides, HRP is an essential peroxidase that contains iron heme prosthetic groups in its polypeptide pockets and can catalyze the oxidation of substrates [102]. HRP was successfully integrated into the Au–BC nanocomposites' nano-network structure while retaining its bioactivity. With a detection limit of less than 1 M, the HRP biosensor allows for highly sensitive detection of H2O2. Many different enzymes could be immobilized using Au–BC nanocomposites, and the resulting enzyme/Au–BC nanocomposites could have a wide range of uses in bio-electroanalysis and bio-electrocatalysis [103]. The researchers have previously demonstrated how to produce porous structures using cellulose nanocrystals (CNCs) and a polymer binder [104]. Polyvinyl alcohol (PVA) is a good polymer choice for CNC film deposition because of its outstanding film-forming characteristics and multiple positive interactions through hydroxyl groups. CNCs have more recently been employed to prepare sensitive materials for bioimaging and biosensing applications [103]. Because both the CNCs and the PVA provide a significant number of surface hydroxyl groups, these scaffolds may easily be derivatized with acrylate functionalities, allowing for the subsequent insertion of a high concentration of luminous sensor motifs via thiolene Michael addition processes, see Fig. 2. The immobilization reaction conditions are light and tolerant, allowing the sensing motif to be selected almost at whim. pH sensors constructed by immobilizing fluorescein have a strong and fast sensitivity to changes in pH. The hydrophilic nature and porosity of the scaffold, as well as the availability of a high number of surface-bound fluorophores, contribute to these properties [105]. For protease wound treatment, a low-density nanocellulose aerogel made of cotton has been used as a transducer biosensor surface. Because of their large surface area and biocompatibility, bacterial CNFs combined with gold nanoparticles have been employed to immobilize heme proteins and enzymes. Hydrogen peroxide biosensors were made using a matrix of bacterial CNF combined with gold nanoparticles. They were discovered to be capable of detecting tiny levels of hydrogen peroxide, according to the research [106]. Weishaupt et al. developed a biosensor for heavy metals. The sensing of cyanobacterial biomolecule C-phycocyanin (CPC) was enhanced with genetic modified bacteria and integrated into CNF films as a carrier material, after which CPC–CNF films were able to detect free copper ions in human blood serum, and heavy metal sensitive fluorescent emission was observed [107]. CNFs in aerogels can also be connected to immobilized antigens or antibodies that bind to an enzyme or fluorophore label that can be used to identify the antibody or antigen [108]. The nanoporous shape of the CNF matrix aids in the retention of the analyte for effective SERS detection. Fluorescent approaches, colorimetric methods, and bioluminescence are examples of optical biosensing techniques [109]. To give CNCs' sensing capabilities, the reactive hydroxyl groups on their huge specific surface area can be coated with sensing nanomaterials. Using

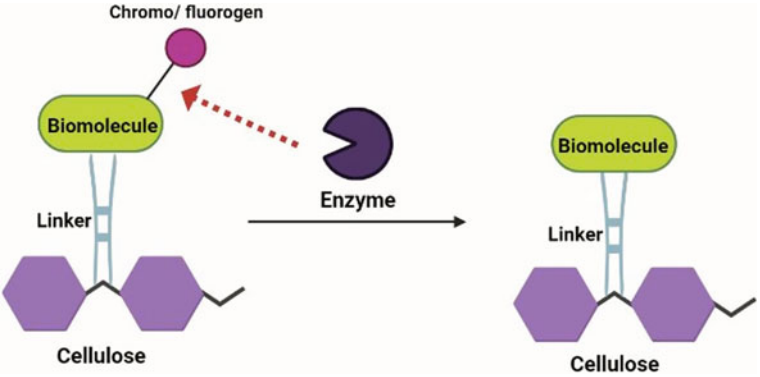


Fig. 2 Cellulose-based enzyme biosensor having a biomolecule-linked surface [114]

carboxylated CNCs as the matrix, Ag–Pd alloy nanoparticles were produced and employed as labels for electrical detection of DNA hybridization [110]. CNC/PVA bio-nanocomposite films' hydroxyl surface groups can react with 2-(acryloxy) ethyl (3-isocyanato-4-methylphenyl) carbamate to complete the nucleophile-based thiolene Michael addition with thiolated fluorescein-substituted lysine [111]. This fluorescent CNC derivative was used to detect protease activity as well as 250 g/mL trypsin, implying that this biosensor could be used in wound diagnosis and other biological applications. n-Succinyl-Alanine-Alanine-Valine-paranitroanilide (Suc-Ala-AlaVal-pNA), a human neutrophil elastase (HNE) tripeptide substrate, was covalently bonded to the glycine-esterified cotton in another application. CNCs are used to create an HNE biosensor [112]. Inspired by the previous research work of Edwards et al., Brumer and co-workers developed recently an alternate strategy toward cellulose-based esterase enzyme biosensors that overcome issues related to fluorophore diffusion after substrate cleavage [113]. In this method, the fluorophore and peptide are positioned differently in relation to the cellulose-linking moiety. As a result, the fluorophore remains attached to the cellulose surface, but the (non-chromophoric) biomolecular recognition element (peptide, lipid, or carbohydrate) is permitted to diffuse away and can be digested eventually [114].

5 Drug Delivery

Nature provides a variety of biomaterials, but none of them meet all of the criteria. Advanced biomedicine has used cellulose, an eco-friendly material-based biopolymer, to meet the majority of market demand while avoiding many environmental concerns [115]. Researchers have tried a variety of ways to use CNCs as drug carriers in the pharmaceutical sector, including direct drug binding, hydrophobic association with drug, covalent attachment of drug, encapsulating drug, and so on [23]. Currently, cellulose-based nanocomposites that are processed into films, foams,

hydrogels, and large-scale materials dominate the field of drug delivery using cellulose nanomaterials [116]. Wound healing is one application where the high surface area of cellulose nanoparticles for higher drug loading and the increased stiffness of the materials due to the presence of cellulose were viewed as beneficial. To transport pDNA and curcumin, for example, nanocomposites based on cellulose nanoparticles and poly(ethyleneimine) PEI were utilized. The fibers were used to treat burns after electrospinning, and animal trials revealed enhanced wound healing [117]. Poly (ethyl ethylene phosphate) (PEEP) was one of the earliest protein-repellent coatings utilized in cellulose nanomaterials-based drug delivery. It was made by ring opening polymerization using propargyl alcohol as the initiator and clicked onto azide-functionalized surfaces [116]. Due to the presence of sulfates in the chosen CNCs, extra negative charges were available to bind doxorubicin, which had a faster release profile at pH 5 than at pH 7. HeLa cells quickly absorbed the drug carriers, and the activity of the pharmaceuticals inside the cell was comparable to that of free drugs, with slightly lower toxicity [118]. Researchers introduced novel cellulose-derived nanoparticles for siRNA delivery into cells. Cellulose nanocrystals in this novel nanovector are coated with a covalently bonded PEI cationic polymer shell. Electrostatic interactions allow these particles to efficiently load siRNA; moreover, complexed siRNA is shielded from RNAse destruction. The CNCs-PEI-siRNA combination was fluorescently labeled with ethidium bromide, indicating that it was integrated into the cells and that it could carry siRNA into the cytoplasm, where siRNA inactivated certain cell-cycle relevant mRNA and caused cell death via the intrinsic apoptosis pathway [119]. Metformin surface-modified cellulose nanofibers (Met-Cel-NFs gel) had viscoelastic qualities that mimicked the surrounding extracellular matrix at the tumor location. After injection into and around the tumor, the Met-Cel-NFs gel can provide a physical barrier. The Met-Cel-NFs gel effectively stopped melanoma cancer cells from migrating [120]. A dual-drug delivery system (DDDS) is proposed to improve chemotherapy efficacy and reduce discomfort associated with colorectal cancer, see Fig. 3. Methotrexate (MTX)-loaded CaCO3 (CaCO3/MTX) and aspirin (Asp) are co-entrapped in alginate (Alg) and sodium carboxymethyl cellulose (CMC) hydrogels cross-linked with Ca2+ in this system. The hydrogels can prevent MTX from being absorbed in the stomach and small intestine, ensuring its potency at the colorectum's target region. More crucially, the DDDS can enable dual pH-responsive medication delivery. Because the pH of the small intestine and colorectum of the human body differs, dual pH-responsive administration of Asp and MTX at the two organs in response to ambient pH is possible [121].

CNFs have been employed as a matrix former for long-term drug administration and as a film for releasing poorly soluble medicines quickly [123]. Other research into the possibility for drug delivery has been published in addition to the work on controlled release of pharmaceuticals to obtain wound healing dressings made from nanocellulose. Amin et al. investigated the feasibility of drug delivery utilizing BNC-acrylic acid (AA) hydrogels. Electron-beam irradiation was used to graft AA onto the surface of BNC, resulting in hydrogels having temperature and pH-responsive characteristics [124]. Other medications, such as famotidine and tizanidine, were also tested using NC as a matrix for controlled drug release [125]. CNC was also used to

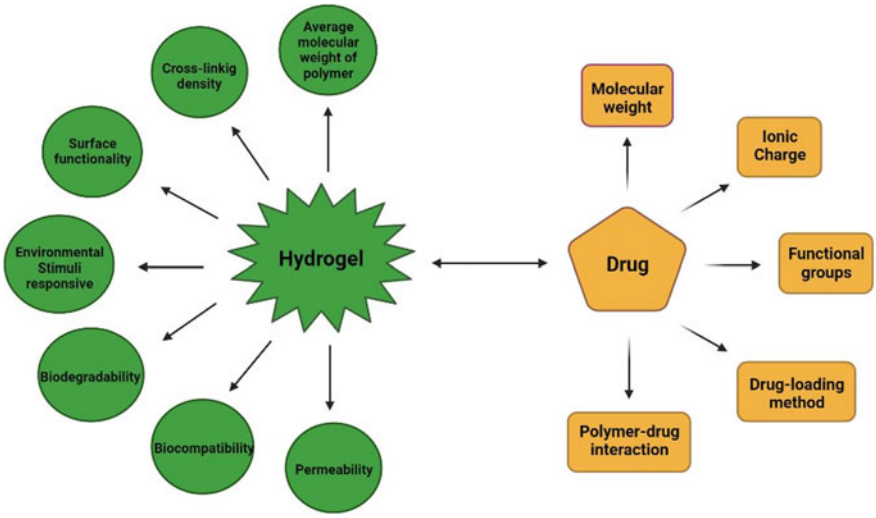


Fig. 3 Characteristics with influence of the effectiveness of controlled drug delivery process [122]

transport medicine delivery systems. CNC was used to stabilize the alginate matrix in order to increase encapsulation and control the release rate of theophylline, which is used to treat respiratory illnesses, as well as to control the release rate of bovine serum albumin (BSA) [126, 127]. Gentamicin-imprinted microparticles produced onto BC nanofibers using in situ graft polymerization might be used to make composite molecularly imprinted polymers' (MIPs) nanofibers. MIP1 composite nanofiber, which was made with the most template molecules, had the highest drug loading quantity. The drug release was more regulated with MIP composite BC nanofibers than with NIP composite BC nanofibers. Furthermore, MIP composite BC nanofibers generated with a smaller amount of template molecule resulted in a smaller burst release [128]. Non-steroidal anti-inflammatory medications (NSAIDs) have been used to reduce inflammation and swelling symptoms for many years. However, it may have a number of long-term negative effects, including gastrointestinal issues such as gastric or duodenal ulcers [129]. In the aqueous media, it is likewise poorly soluble. As a result, localized or targeted distribution of NSAIDs is a new technique for reducing these downsides [130]. Non-steroidal anti-inflammatory drugs like naproxen, indomethacin, ibuprofen, and sulindac are used to treat pain. They have been successfully integrated into electrospun cellulose acetate (CA) nanofibers and employed as a novel delivery mechanism topically [131]. Naproxen has a limited bioavailability and is not absorbed via the skin. By converting it to ester prodrugs like methyl ester, ethyl ester, and isopropyl ester and incorporating it into electrospun CA nanofibers, it can be used as an effective transdermal. These medications had

Table 1 Nanocellulose-based drug delivery systems

Drug delivery system	Nanocellulose	Co-material	Model drug	Drug uses	Results	Refs.
Hybrid nanoparticles	Cellulose nanocrystals (CNC)	Alginate	Silybin	Antibiotic against Mycobacterium tuberculosis	Sustained drug release	Thomas et al. [137]
Self-stabilized pickering emulsion	CNC	Alginate		Anti-tumor	Silybin's dissolving rate and oral bioavailability have both improved	Yang et al. [138]
NP/CNC nanocomposite	CNC, oxidized CNC	Chitosan	Repaglinide	Anti-hyperglycemic	Efficacy of drug entrapment is high. Drug release that is both sustained and controlled	Abo-Elseoud et al. [139]
Micro-hydrogel composite	Cellulose nanowhiskers (CNW)	Starch	Vitamin B12		Sustained release of vitamin B12	Hasan et al. [133]
Cellulose nano-paper and nano-foam	Cellulose nanofibers CNF	Starch	Indomethacin	Non-steroidal anti-inflammatory drug (NSAID)	Sustained drug release due to high porosity	Löbmann et al. [140]
Aerogels	CNF	Polyethyleneimine	Sodium salicylate	Wound healing agent, antidiabetic, anticancer	High drug loading. Long-term drug release	Sarkar et al. [133]
CNF/Chitosan transdermal film	CNF	Chitosan	Ketorolac tromethamine	Non-steroidal analgesic	Sustained drug release	Abba et al. [141]
BC membranes	BC		Crocin	Antioxidant	Stable and prolong drug permeation	Abba et al. [142]

(continued)

Table 1 (continued)

Drug delivery system	Nanocellulose	Co-material	Model drug	Drug uses	Results	Refs.
CNC film	CNC	Polyvinyl alcohol	Curcumin	Antibacterial	Drug release that is both controlled and long-lasting	Tong et al. [143]
Magnetic NPs	CNC	Tris(2-aminoethyl) amine, Fe3O4 NPs	Methotrexate	Anticancer	High drug loading, drug release that is both controlled and long-lasting Drug release dependent on pH responsiveness	Rahimi et al. [83]
Nanocomposite hydrogels	CNC	Poly (acrylamidoglycolic acid)	Diclofenac sodium	Non-steroidal anti-inflammatory drug	Excellent mechanical and viscoelastic qualities, as well as a pH-sensitive nature, release of drugs under strict control	Hasan et al. [133]

a sustained release over 144 h and outstanding compatibility with uniform dispersion within the polymer fiber, according to a drug release study [132]. Nanocellulose and its derivatives are extensively employed as drug excipients (e.g., thickeners, emulsifiers, binding agents, film formers, stabilizers, surfactants, suspending agents, and lubricants) and as drug delivery matrices (carrier system) in which a drug (including insoluble medicines) can be loaded [133–135]. One of the key advantages of nanocellulose-based drug delivery systems is long-term drug release, see Table 1. Water retention, film formation, adhesion augmentation, and rheology control are all strategies that nanocellulose can use to alter drug release [136].

6 Tissue Engineering

Tissue engineering is a safe and effective way to repair or restore organs that have been damaged or destroyed. A scaffold is built in a three-dimensional medium suited for seeding and developing cells in this method [144]. Hydrogels, a common type of biomaterial used in tissue engineering, are made up of a water-swollen cross-linked network with highly entangled chains that produce a slow rate of polymer disintegration in water. Hydrogels are commonly employed as a 3D scaffold due to their high oxygen permeability, ease of manufacture, and appropriate viscoelasticity. In addition to PLA and PVA (synthetic biopolymers), the most common natural

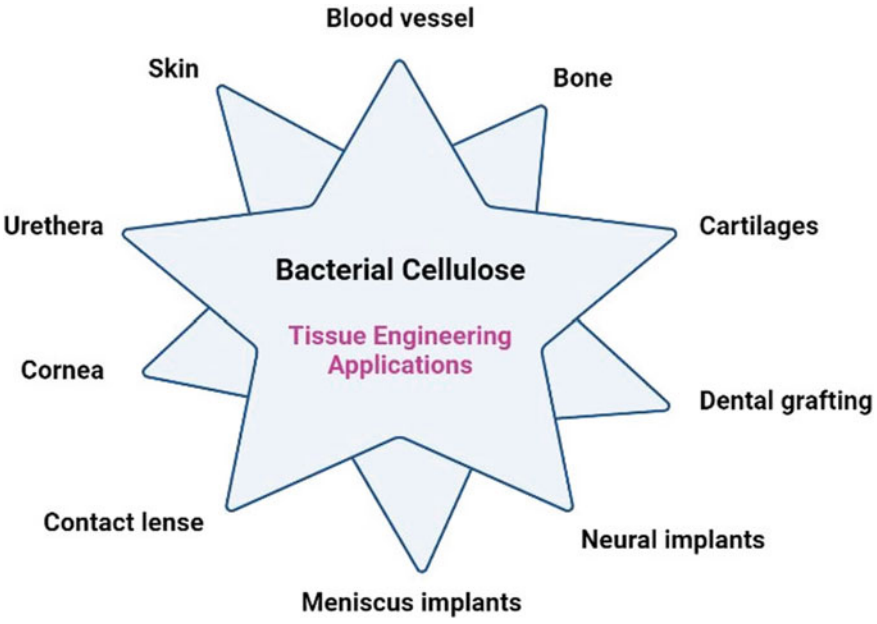


Fig. 4 Schematic illustration of biomedical engineering purpose of BC [175]

polymers, collagen and alginate, have been employed as hydrogels in tissue engineering [145]. Continuous attempts are being undertaken to find effective biomaterials that can aid in the regeneration of biological tissues that have been harmed. Metals and graft are being phased out in favor of polymer-based structures, which have demonstrated excellent performance [146]. Dense films and membranes, hierarchical three-dimensional (3D) porous constructions (micro/nanofibers mats, foams, and sponges), and hydrogels are examples of CNC-based functional biomaterials for tissue engineering [147]. To build a totally bio-based scaffold in vascular tissue engineering, CNCs were inserted in cellulose acetate propionate as a matrix [148]. Myoblasts (muscle cells) were able to respond to tunicin CNCs' submonolayer surfaces with a high degree of orientation [149], resulting in highly orientated multinuclear myotubes [150]. By chemically grafting low molecular weight PCL diol onto CNCs [151, 152], fibrous nanocomposite mats [153], or uniaxially aligned cellulose nanofibers, low molecular weight PCL diol was employed to reinforce poly(-caprolactone) (PCL) nanofibers [154]. The nanofibers were particularly effective for various artificial tissues or organs because of their improved mechanical qualities and thermal stability, as well as their non-toxicity to human cells and powerful effect on directing cellular organization. In a whole bio-based technique for the fabrication of reinforced injectable hydrogels, nave CNCs and aldehyde-functionalized CNCs (CHOCNCs) were also used as nanofillers [23, 155]. There are now a variety of approaches for fabricating suitable cellulose scaffolds for use in hard and/or soft tissue regeneration. Electrospinning is one of the most commonly accepted ways for fabricating fibers with diameters ranging from nano- to microscale with applications in numerous industries of technology [156]. The most significant benefit of this technology is that it can manufacture nanofibers with controlled diameter, porosity, and morphology that replicate the extracellular matrix (ECM) of native tissue found in the human body [157, 158]. The nanofiber aids in the adhesion, migration, proliferation, and differentiation of native cells, which are in desperate need of regeneration, in addition to providing structural support and topographical and biochemical signals [159]. Cellulose is a naturally occurring polymer with superior biocompatibility, cellular mimicry, and hydrophilic characteristics than its proportional homologue, see Fig. 4. We used alkaline deacetylation to regenerate acetate-free nanofibers from as-spun nanofibers. By reducing adsorbed Ag ions on sodium borohydride, the resultant cellulose nanofibers previously loaded with hydroxyapatite (HAp) were immobilized using silver (Ag) nanoparticles (NPs). The MTT experiment on chicken embryo fibroblasts revealed that these nanofibers were cytocompatible. After cell culture, SEM of the materials revealed that these composites allowed fibroblasts to proliferate over and inside the nanofiber network, and increasing HAp concentrations levitated excessive apatite production as well as boosted cell development [160]. For cartilage tissue engineering, starch/cellulose nanofibers' composites with suitable porosity pore size, mechanical strength, and biodegradability have been described. Film casting, salt leaching, and freeze drying were used to create porous thermoplastic starch-based composites [161]. All of the samples showed a porous morphology that was interconnected; however, when the sodium chloride ratio in the salt leaching was raised, the pore interconnectivity increased. Scaffolds with a

total porogen concentration of 70% had appropriate mechanical characteristics for cartilage tissue engineering. By adding 10% cellulose nanofibers to nanocomposites, the water uptake ratio was dramatically improved. After more than 20 weeks, the scaffolds were partially degraded because of a low in vitro breakdown rate. The integration of nanofibers in the starch framework increases cell adhesion and proliferation, as demonstrated by the cultivation of isolated rabbit chondrocytes on the manufactured scaffold [162]. Because of its exceptional biocompatibility and bioactivity, hydroxyapatite (Ca10(PO4)6(OH), HA), a natural inorganic component of hard tissues, has been widely employed for bone repair, fillers, and substitute [163]. The dispersion of hydroxyapatite (HA) nanoparticles in aqueous solution was nanofibrous 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO)-oxidized bacterial cellulose (TOBC). After reacting with the TEMPO/NaBr/NaClO system at pH 10 and room temperature, the surfaces of TOBC nanofibers were negatively charged. The colloidal stability of the dispersion solution and the chemical alteration of the fiber surfaces validated TOBC as a suitable HA dispersant. Because of the increased cross-linking of gelatin, both the Young's modulus and the maximum tensile stress rose as the amount of gelatin increased. Furthermore, the well-distributed HA resulted in a denser scaffold structure, which increased the Young's modulus and maximum tensile stress. Calvarial osteoblasts were incubated with the well-developed porous structures of the HA–TOBC–Gel composites. The HA–TOBC–Gel considerably increased cell proliferation and differentiation, indicating that the material might be used in bone tissue engineering scaffolds [164]. Tissue engineering uses 3D scaffolds as an artificial ECM for cell seeding, proliferation, and the generation of new tissue. One of the benefits of biopolymers (nanocellulose, collagen, xylans, and others) for scaffolds is their biological recognition, which can help cells adhere and function better. The scaffold should biodegrade at the same rate as new tissue in the body, allowing it to be safely removed [165]. For skin tissue engineering, CNC and CNF have been combined with different polymers to build constructs that have biocompatibility, mechanical, thermal, and swelling qualities similar to natural skin. In comparison to plain PLGA, CNC was inserted into polylactide–polyglycolide (PLGA) to form PLGA/CNC membranes by electrospinning, which improved cell compatibility, adhesion, spreading, and proliferation of fibroblasts [166]. PVA, GelMa, collagen, gelatin, and chitosan have been combined with nanocellulose to generate structures that mimic real skin in terms of cell adhesion, growth, and metabolization [167, 168]. Nanocellulose can be used to regulate the porosity, mechanical strength, orientation, and flexibility of neural tissue engineering scaffolds. After some damage, neural tissue has a limited ability to self-repair and regenerate. Nanocellulose scaffolds, alone or in conjunction with carbon nanotubes, direct and promote brain cell development by maintaining the axon channel and stimulating neuronal activity [169]. Stability, stretchability, flexibility, and cytocompatibility are all requirements for cardiac tissue engineering scaffolds. CNF produced using a TEMPO-mediated oxidation or acetylation method had good biocompatibility with cardiac myoblast cells and showed strong fidelity in both wet and dry conditions [170]. The goal of hepatic tissue engineering is to create functional liver organs that can be transplanted. The development of hepatocyte HepaRG and HepG-2 cells is aided by CNF

hydrogels, which facilitate 3D hepatocyte culture. Three-dimensional bioprinting was employed to replicate hepatic structure with CNC/alginate bioinks, resulting in high shape fidelity and minimum cell mortality [171]. Tissue engineered heart valves are also being created utilizing biopolymers to eventually replace mechanical counterparts since they offer advantages in terms of durability, the ability to grow, repair, and remodel cardiac tissue, and the ability to grow, repair, and remodel cardiac tissue [172]. Electrical stimulation is a problem that only a subset of cell types, such as neurons and myocytes, faces in nerve tissue engineering. As a result, biomaterials that are electroactive, flexible, and 3D nanostructured are needed. Carbonization or cellulose scaffolds coated with conductive materials like poly (3,4-ethylenedioxythiophene) (PEDOT) and multi-walled carbon nanotubes can be employed to meet these parameters [173, 174].

7 Anti-aging

Aging is biological progressive process in an organism that results in degenerative changes in skin, muscles, and over all body postures that result in death with the passage of time. Research now days on global scales is based upon finding and applying them as anti-aging natural compounds that are bio-based. In fear of death, to prevent early aging and other diseases, many researchers have documented many possible medications in Egypt, India, China, and Greece [176]. Aging causes many age-related diseases like diabetes, urinary disorders, stroke, and hepatic disorders. Almost 2000 years ago, a classical theory about aging was proposed by Huang Di Nei who was skilled father of Chinese traditional medicine [177]. Delaying aging by healthy life style can delay in age-associated problems and diseases [178]. Nowadays, increasing numbers of people are in facing the early aging of their skin due to different factors [179, 180]. Premature aging is great concern for every one as all the people want to look young and they adopt different approaches to stop aging [181]. Cosmetics, health care, fitness are new well-organized and growing market. Ecological and eco-friendly trends are forcing population to use bio-based active compounds that are helpful in anti-aging process [182]. Morphology of skin and apparent physiology is the first thing that a change with time and deterioration in skin with the age is normal process. Deterioration in skin results in imbalance of con homeostasis and thermoregulation [183]. Skin is very sensitive part of our body; it is directly exposed to outside of environment, ultraviolet radiations and other factors damage the lipids, DNA in skin cells along with harmful impacts on protein part of skin and approaching other body parts that may have serious hazards in future like cancer and early aging [184]. Changes due to epigenetic mechanism are numerous for promoting aging, transcription factor issues, histone protein marks, and methylation of DNA [185]. Telomere syndrome that is inherited in some patients caused them premature aging [186]. Mutations caused by internal and external sources in human body are leading causes of aging, as mutation are changes in DNA material that can bring a lot of detrimental effects because DNA is regulator of all cellular

activities [187]. Threats to human genome include errors in DNA replication, reactive oxygen species (ROS), chemical agents, biological factors, UV radiations, point mutation, chromosomal gains, gene disruption, and hydrolytic reactions that are spontaneous [188]. In humans, it has been observed that defected genome promotes aging while maintenance of DNA found to be supportive in delaying the aging process [189]. Over production of radicals inhibits the working of antioxidants and cells are degenerated, resulting in oxidative stress and DNA damage leading to aging [190]. Cellulose is organic polymer that is most abundant compound on earth that is why it is easily available [191]. A. J. Brown discovered cellulose from bacteria in 1886 during the fermentation process of vinegar [192]. There are several polysaccharides but most distributed and widely found are chitin that is found in fungi and cellulose in plants. Plant cell wall is made up of cellulose, so raw material for cellulose can be obtained through wood [193, 194]. In recent years, biomedical application of cellulose has become very popular due to its enormous application in cosmetics, anti-aging, etc. Increasing demand is due to look young, so enormous researches have been conducted to find out the potential of safe methods for treatment [195–197]. Cellulose obtained from natural sources are low cost that can be used on larger scales for biomedical applications [198]. Cellulose detoxifies the detrimental effects of environmental impacts on human body [199]. Cellulose helps in porosity that is required for connection of targets to serve medical complications [200], and cellulose biopolymers are very safe with minimum side effects and eco-friendly in nature that is reason of high demand in markets. Synthetic chemicals have wide range of side effects [201–204]. Marine and ocean water bodies are great source of biopolymers like cellulose and chitin. Most of the raw material is obtained from brown algae, red algae, green algae, and other aquatic plants are primary producers [205]. Algae are photosynthetic and great producer of biomass. Cellulose obtained from algal sources has great medicinal benefits as they are used as anti-infection, skin infection, and anti-aging [206]. Cellulose-derived chemicals decrease the production of free radicals protecting negative mutations to DNA and hence resulting in healthy body. Reason for healthy life is perfection and stability of its DNA without negative mutations [207]. Cellulose of plants and other chemicals that are high in phenolic chemicals and compound like chlogenic acid, gallic acid, rosmarinic acid, vanillic acid, genistein, caffeic acid have their active role in protection against high solar radiations and ultimately minimize aging factors that is why such plant-derived chemicals are in high demand in medical industry [208–211]. Natural bio-based compounds like cellulose masks were tested for trials to check the medical application as anti-aging and anti-wrinkle formula for biomedical applications, and result proved that cellulose is best in their anti-aging potentials. These mask have direct actions against negative changes that are due to different environmental factors [212]. Most beneficial cellulose for biomedical applications is obtained through bacteria that has high range of quality and results. Cellulose obtained from bacteria source is unbranched polymer with chemical purity [213, 214]. Bacterial cellulose is biocompatible in less expensive [215]. Biosynthesis of bacterial cellulose is achieved through polysaccharides that are excreted, carbon-derived sources of culture medium [216]. In medical field, diagnosis of any disorder is first step toward the procedure of cure; without

proper diagnosis, there are no drug and treatment. Bacterial cellulose is very important because they are being used for advance studies in diagnostic medicine [2]. Cellulose obtained from bacteria (BC) is biosynthesized polymer. *A Gluconacetobacter xylinus bacterium* is best known for production of cellulose [217]. Including Aerobacter [218] and Agrobacterium [219], all are involved in the production of cellulose that contains many biomedical properties like water holding, best mechanical properties, permeability, and biodegradability [220–223]. Properties of bacterial cellulose (BC) were reported in treatment of many disorders; especially, it is effectively used in anti-aging applications, as this is involved to scavenge all negative changes in the cells that are produced through inside or outside factors along with this regularize normal functioning of cell [224–226]. Many other researchers have reported bacterial cellulose (BC) as a supportive agent in drug delivery system that is the basic quality that makes bacterial cellulose to be used as anti-aging chemical. Drug delivery is important quality of any chemical because it is main requirement for curing [227–229]. It has been extensively studied to serve as skin protective agent from many harmful environmental fluctuations, as environmental fluctuation has direct effect on skin and ultimately negative physiological impacts on whole body. External environments induce changes in internal chemistry of human and though proved to be strong factor for aging and other disorders [230, 231]. Bacterial cellulose contains active chemicals that are directly working as anti-aging agents, and these chemicals are bioactive and directly involve in healthy cellular activities as they maintain the internal atmosphere of the cell at equilibrium that bring positive result for tissues and organs for healthy body [232]. Cellulose membrane of bacteria is very best for delivery of many active chemical compounds like moisturizers, anti-wrinkle, and protective agents for skin aging. Along with this, bacterial cellulose has vast range of application in cosmetics preventing skin from dehydration and controlling the sebum [233, 234]. In addition, with bacterial cellulose, other biopolymers are also potentially involved in UV protection, anti-aging, and antimicrobial activities. It has been experimentally proved that cellulose has UV shielding and age delaying potential [235]. Cellulose is involved in regeneration of epithelial cells [236]. Regeneration of nerve cells [237] helps in chemotactic responses for macrophages [238]. Regeneration of new tissues, wound healing, and scar removing change the look young [239]. Directly ability of interactions of cellulose with cells, inhibits carcinogenic effects, promotes new cell division, remove harmful substances that causes aging [240, 241]. In past years, people are in search of medications that help them to look young and fit and slow down the process of aging. People mostly use drugs that have a lot of harmful side effects. Bio-based alternative medicine is future of industry that is very safe and has multi-benefits [242]. Scientific field is approaching cellulose as a anti-aging potential because this cellulose has numerous direct and indirect functions that collectively help in anti-aging process [243]. As cellulose is involved in numerous biomedical applications which help as antioxidant, for example, cellulose and its derivatives are involved in tissue engineering [244], inhibit oxidants, and help in wound healing [245], key interest of research as a potential drug delivery polymer [246]. All these applications and much more biomedical

services make cellulose organic material of interest. However, production of large-scale cellulose for biomedical applications needs attention because huge demand can be approached by keeping in mind the raw material, cost, and efficient usage [247].

8 Antioxidant

Cellulose is abundantly found polysaccharide on earth. There are different sources through cellulose which can be obtained like plant cell wall, algae, tunicates and bacteria [248]. Bio-based chemicals and compounds are getting fame in new research. Cellulose is widely distributed polymer. These carbohydrates are long-chain polymers that are involved in antioxidant and drug delivery systems, and these cellulose polymers are much more effective than synthetic chemicals with low cost, healthy environmental role, and no side effects in biomedical applications [193, 194]. Natural cellulose has unique capacity of flexibility and exploits in different hierarchical forms [249]. Cellulose is biopolymer that has potential to work alone and in combination with other molecules. Nanocrystals of cellulose are current target of study for biomedical applications and commercialization as they are involved in drugs and delivery systems of gene [250]. Cellulose being organic polymer and its derivatives represent large portion of biomedical industry as they are low-cost antioxidants that have unique properties like soluble in water, organic solvents, tissue engineering, hydrogels, and drug delivery systems. Organic cellulose is polymer that is easily biodegradable [251]. Cellulose is polysaccharide, different polymers are extracted from natural cellulose like carboxymethyl cellulose, hydroxypropyl-methylcellulose, methylcellulose, and hydroxyl-ethylcellulose, and they are favorable due to mechanical strength, water absorbance, antioxidant, and many other biomedical applications in different research and medical sectors [252, 253]; these cellulose derivatives have biocompatibility, eco-friendly, biodegradability [254, 255], and huge number of applications in biomedical industry [256, 257]. Cellulose are non-toxic and less expensive to manufacture and modify as antioxidant [258]. In past few decades, there is huge demand of cellulose for biomedical applications [259, 260]. Cellulose shows extraordinary potential of work as antioxidant as they hit the target area precisely [200]. There is an increased trend toward the plant-based extracts to be used as antioxidant [261]. Wide range of plants for extracting cellulose have been investigated to find out these potential biomedical applications to serve mankind. These plants include cotton as cotton is pure form of cellulose [262, 263] leaves of pineapple [264], corn cell wall [265], hemp plant varieties [266], straws of cereals [267], waste of potato, especially peel [268], and biomass of oil extracted from palm species [269]. Oxidative stress is harmful for all living organisms, especially in human, and cellular homeostasis disturbs and causes serious complications including inflammations, aging, negative physiological changes, etc. [270–273]. Autoxidation is deterioration in biological system of any organism result in cell damage and serious diseases, and autoxidation involves series of reactions in which oxygen that comes through atmosphere react with lipids systems [274]. Bacterial cellulose is famous

for research perspectives; it has great potential for antioxidant and diagnostic field of diseases. It is highly pure and can be modified for further uses. Skin burn is alarming and can lead to death; applying bacterial cellulose invades harmful microorganisms and induces changes for regeneration of skin. Biomedical field is very important and applications of bacterial cellulose for drug delivery, antioxidant, and tissue culture are well known, and progress is being made to use cellulose for more studies as antioxidant role is of great importance as antioxidants are actively required to counter detrimental effects of internal and external harms [275].

9 Dentistry

More attractive orthodontic appliances have been increasingly popular in recent years. Labial fixed appliances are still the most popular fixed appliances, and there are two types of attractive brackets available today: ceramic and polymeric. While both have good looks when it comes to location, they both have flaws when it comes to clinical application [276]. In the laboratory investigation, cellulose acetate was electrospun after being dissolved in an acetone and dimethylacetamide solvent solution. To create a self-supporting nanofiber mesh, the spinning parameters were optimized and lithium chloride was added to the solution. After that, the mesh was silane coated before being infiltrated with epoxy resin or an unfilled Bis-GMA resin. The manufactured samples' flexural strength was tested and compared to that of unfilled resin samples. Electrospun cellulose acetate nanofibers in the 286 nm range were successfully electrospun using this technology [277]. In biomedical applications, biopolymer gels are widely employed. Tissue engineering, wound dressing, dentistry, and in particular, the fabrication of periodontal regeneration membranes using biopolymers and nanoparticles are examples [278]. There are numerous distinct commercial products of biopolymers, such as polylactic acid, collagen, and gelatin, depending on the diverse raw materials and production processes [279]. The polylactide and polyglycolide membranes (Atrisorb® and Resolut LT®), bovine type I collagen membrane (OsseoGuard™), porcine type I and III collagen membrane (BioGide®), resorbable collagen membrane (Biomend®), and gelatin-based sponge (Gelfoam®) are all examples of periodontal regeneration membranes made of collagen [280]. Hydroxyapatite is a biocompatible, bioactive, osteoconductive, nontoxic, non-inflammatory, and non-immunogenic mineral that is found in the bones and teeth of vertebrates [281]. Hydroxyapatite can be made in a variety of ways, including dry, wet, and high-temperature processes [282]. Tailor-made hydroxyapatite nanoparticles can be synthesized by using diverse technologies and correctly modifying operational parameters. Chemical or natural resources can be used to make the precursor for manufactured hydroxyapatite [283]. Although the pure form of the precursors may usually improve purity, hydroxyapatites obtained from natural resources are more cost-effective and have superior metabolic activity and bioactivity than synthetic counterparts [284]. The mechanical strength, biocompatibility, and

bioactivity of hydroxyapatite can be improved by combining it with organic or inorganic substances, as well as some specific properties [285]. The water contact angle, mechanical strength, and stiffness of polyurethane membranes manufactured with titanium dioxide (TiO_2) and hydroxyapatite are all higher than those without TiO_2 and hydroxyapatite. Cell adhesion, viability, proliferation, alkaline phosphatase (ALP) activity, and calcium content are all improved [286]. Biocompatibility and osteoconductivity of guided tissue membranes embedded with hydroxyapatite are good, and they can create favorable conditions for wounded bone repair. Hydroxyapatite has the capacity to regenerate dental tissue [278]. The most advanced materials are carbon nanotubes and graphene. When compared to carbon nanotubes and graphene, which are being researched for usage as nano-reinforcing materials, one of the advantages of CNF is that it can maintain high transparency with reduced visible light spectrum absorption. The creation of new dental materials is a never-ending pursuit [287]. Biocompatibility or toxicity, comparable to antibacterial property, is an important question for biomedical materials. Diverse studies produce different results in terms of cellulose biocompatibility, which can be attributed to the wide diversity of methodology and sample preparation processes used. Unfortunately, direct biocompatibility studies of CNCs and CNFs are relatively uncommon [288]. CNFs are believed to have a low environmental effect and a high level of safety because they are naturally occurring compounds made up of glucose subunits. As a result, there are several researches relating to the use of CNFs and CNCs in biological fields such as dental repairs [289].

10 Conclusion and Future Perspectives

In conclusion, cellulose and its derivatives have proved their excellent role and effectiveness in different biomedical applications. That is why scientists could rely on these biodegradable and biocompatible materials in their research in the biomedical field as the core material or carriers or ligands. For future, researchers can discover more about the application of cellulose and its derivatives in different scientific fields such as environmental and water treatment disciplines as they are available, cost-effectives, biodegradable, and consequently eco-friendly materials.

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Pharmaceutical and Biomedical Importance of Regenerated CEL and Composites in Various Morphologies

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Abstract Natural biopolymers or biodegradable polymers are the focus areas of researchers as per environmental concerns and wider applications in industries, particularly in the biomedical sector. Cellulose (CEL) is a biopolymer found in almost every plant cell wall that is regenerative, biocompatible, non-toxic, and reusable. It is the most abundant polysaccharide on Earth. It might be discovered in a wide range of areas, including algae, bacteria, and worms, and both plant and wood cell walls have known CEL-containing species. It seems to be a versatile material with adaptable properties that could be used to create biomaterials and tissue engineering. Biomaterials produced from CEL have a lot of benefits over synthetic materials. This inevitable enormous amount naturally facilitates the discovery of new application domains for this adaptable content. This chapter has discussed CEL and its derivatives, as well as its biochemical and structural characteristics and applications including tissue engineering, wound healing, and medicinal delivery systems.

Keywords Cellulose · Tissue engineering · Wound dressing · Drug delivery system

1 Introduction

Cellulose (CEL) is the most prevalent carb on the globe. It exists in a variety of locations, including the wood and plant cell walls, a few algae and bacteria, and tunicates, the only organisms known to contain CEL. Naturally, this plentiful supply encourages the creation of new uses for this versatile material. It is a versatile material having customizable properties that might be used to produce biomaterials and tissue engineering (TENG). Biomaterials made from CEL have many benefits

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over synthetic materials. Innately, this plentiful supply inspires the development of innovative utilizations for this flexible material [1].

Bio-based materials are picking up steam in biomedical disciplines such as TENG, WL, and medication delivery, leading to a rise in demand. In contrast to synthetic polymers, polysaccharides, which are units of biopolymeric long-chain carbohydrates typically made of monosaccharide molecules, are organic resources with great implications in biomedical applications. Based on their wide occurrence in nature, the most abundant chitin and CEL are valuable ecological biopolymers among the different kinds of polysaccharides. Chitin is produced primarily by lower animals, whereas CEL is primarily produced by plants and trees [1, 2].

Based on its distinct mechanical and physical properties, CEL and its derivatives have drawn considerable interest as biocompatible polymers for biomedical purposes. CEL produces capabilities, versatility, and high specificity using its hierarchy [2, 3]. Additionally, it is cheap, biodegradable, and lightweight [4]. Cellulosic materials' ability to precisely manage porosity and interconnectivity makes them ideal for biomedical applications [5].

An overview of the biomedical field of CEL in areas like TENG, WL, and various drug delivery systems is given in the current chapter.

2 CEL

The majority prevalent polysaccharide and organic molecule on Earth are CEL, an unbranched, natural polymer formed of C6H10O5n glucose units that are reiterated [6]. In CEL, a homopolymer of carbohydrates is made of bounded D-glucopyranose units together by 1, 4-glycosidic linkages. In CEL, the -CH2OH groups alternated immediately above and below the axis of rings, resulting in longer, unbranched chains. Because CEL molecules do not have side chains, they can form incredibly strong structures [7, 8]. Algae, green plants, and oomycetes all appear to have CEL as part of their main cell walls [9]. Stronger 14 glycosidic connections between individual CEL strand units are used to connect CEL chains as they pass through numerous crystalline and chaotic zones. In the crystallized portion of a CEL fibril, the CEL chains are magnificently associated [10].

2.1 Sources of CEL

CEL can be founded that used a range of resources and strategies that are simultaneously regarded as synthetic as well as natural. Native CEL, which is CEL made by plants, comes in two crystal kinds: CEL I and CEL II [11]. When Aqueous sodium hydroxide is used to treat CEL I, CEL II, a crystalline form that typically occurs in marine algae, is created [12, 13]. CEL I is the least thermodynamically stable of the four polymorphs of crystal, CEL II while CEL III and IV are the most stable. CEL I

and CEL II are processed by aqueous ammonia to generate crystalline CEL III [14, 15], and when CEL III is heated, crystalline CEL IV is produced [16].

Due to the presence of epidermal cell membranes, CEL is often found in nature as microfibrils in algal tissues, wood, and plant cell walls as in Fig. 1. It can also be created by bacteria as networks of nanofibers. Fibrils, fibril aggregates, nanocrystalline, and nanoscale disorganized subject areas are examples of various leveled structural designs that are advantageous for cellulosic materials as per Fig. 1. Superfine fibril bundles and aggregates make up CEL's extensive and varied structure. Multiple CEL chains are present in ultrafine fibers. Narrow disordered (amorphous) and reciting large structured (crystalline) areas constitute each fibril, relying on the synthesis source, with cross-sectional sizes varying from two to twenty nm [17]. Natural sources of CEL are natural fibers. Sources for natural fibers include plants, animals, and minerals. Depending on where they came from, natural fibers can be categorized. Cotton, flax, jute, sisal, hemp, and ramie are some dietary fiber. Paper and cloth are produced using CEL fibers. The following subcategories of this fiber are also possible: Cotton, flax, and hemp are the most popular vegetable fibers, but sisal, jute, kenaf, and bamboo are also used [18, 19].

Most synthesized or man-made fibers are made from petrochemicals and other synthetic materials. However, natural CEL is used to make some synthetic fibers, including modal, rayon, as well as recently developed Lyocell. The two types of CEL-based fibers are modified CEL (such as CEL acetates) and regenerated or pure CEL (such as from the cupro-ammonium process). There are 2 kinds of fiber categorization used throughout plastic composites: 1. Short fibers with a typical aspect ratio of twenty to fifty, also referred to it as fibers (the proportion of fiber length to diameter) and 2. long fibers, also referred to as continuous fibers, typically have an aspect ratio among both 200 and 500 [20].

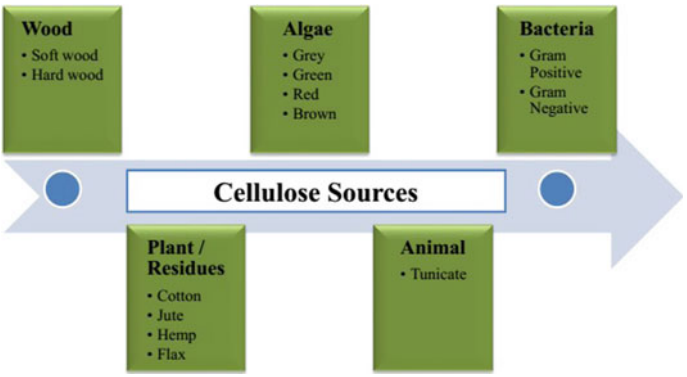

Fig. 1 CEL Sources [1]

3 Biomedical Application of CEL

3.1 Application in Tissue Engineering

In the interdisciplinary field of TENG, ideas from engineering and life sciences are combined to create intelligent biological substitutes that can rebuild, preserve, and augment ruptured tissue's capabilities. In the field of TENG, biomaterials are frequently used to build structures for specific medical interventions. The human body's living biological components, such as physiological fluids, biomolecules, tissues, cells, and organs, will be exposed to these structures. Component for regenerative tissue ought to have optimal physical qualities, such as compression resistance for bone TENG or mechanical properties for repairing soft tissue and artificial blood vessels. Synthetic aspects, like the materials' surface properties, but on the other side, are crucial, and components must be chosen for specific application reasons. For example, without sacrificing the mechanical qualities of tissue scaffold fabrication, nano-cellulosic materials can have their porous structure, width, and interconnectivity altered [21].

CEL should have the same mechanical behavior as real tissue to be utilized as an excipient or primary material of implant in TENG, encourage porous scaffold structures, or aid osteoblastic bonding sites, and fibroblasts. For TENG, hydroxyethyl CEL, CEL acetate, hydroxy CEL, carboxy methyl CEL, methyl CEL, and sulfate are the most frequently utilized CEL analog. The development of a biologically appropriate platform is among the most frequently utilized biomaterial applications in TENG [1]. Animal cells are hydrophilic and have low capabilities for quasi-protein adsorption, which prevents them from adhering with relation to cellulosic surface used in synthetic tissue scaffolds. On the contrary hand, this same inclusion of matrix ligands in cellulosic materials can enhance cell attachment to substrate surfaces. For instance, ionic charges can be used to adsorb collagen on the surfaces of CEL membranes, facilitating cellular attachment [22].

CEL can be modified to work in the brittle and mechanically demanding setting of bone [23–25] because the natural bone is highly porous and approaches for producing for bone TENG; porous structure organic substances are essential. One way to make pores is by laser irradiation of CEL acetate electrospun fibers. Pore diameters of 50 to 300 m can be created without harming the surrounding material [26]. These frameworks can undergo significant nanosized processing to mineralize to a degree resembling that found in vivo [26, 27]. The granular calcified structures promote the attachment and expansion of osteoblasts. Porous mineral substrates promote cell density and osteoblast adhesion at the site of the pore [26]. Pure bone is primarily constructed of minerals as well as collagen that resemble hydroxyapatite in structure [28]. It is critical for bone TENG to mimic this complicated makeup. The CEL nanofibers/hydroxyapatite composites' porosity, compressive strength (0.1 up to 12 MPa), compressive modulus (6 up to 330 MPa), and biocompatibility can be used to mimic natural bone [28–32]. In vivo investigations with CEL scaffolds mixed with gelatin-based hydrogels that have been then covered

by hydroxyapatite found that this technique aided in the production of new bone [32]. Electrical stimulation is a problem that only a fraction of cells, including myocytes and neurons, face in nerve TENG. Thus, the need for three-dimensional nanostructured, electrochemically active, as well as versatile biopolymers. In combination with carbonization, CEL scaffolds covered wi3,4-ethylene dioxythiopheneke as poly(3,4-ethylenedioxythiophene) (PEDOT) and multi-walled carbon nanotubes can all be employed to meet these needs. Such components are biocompatible, support neuronal differentiation, and have tunable pore inner diameter, electrical conductivities, and mechanical behavior [33, 34]. The use of CEL constructions as nerve-guiding sciatic nerve conduits abnormalities within rats has been demonstrated. According to the findings of this investigation, CEL-based citalopram can greatly affect the sciatic nerve's functioning [35].

In the lack of protein, positively charged bacterial CEL has also been used to promote cell attachment [22]. A biopolymer with enormous potential for use in dental and oral applications is bacterial CEL [36]. Recently, functional bio polymeric-based materials are being used as viable technique for creating, mending, and regenerating operational organs and tissues in human. These materials are both affordable and user-friendly. It has been suggested that cellulosic composites be used in the creation of scaffold structures that could be transplanted in patients to replenish failing or sick organ systems. Additionally, a key factor in enhancing the characteristics and long-term biocompatibility of TENG biocomposites composites is the selection of the proper reinforcement material. CEL materials are now a quickly developing field in biocomposites because of their potential to improve properties [37, 38]. For instance, it has recently been demonstrated that cellulosic fibers, because of their distinct structure, increase the strength and power of biopolymer scaffolds in bone TENG applications [39].

Nanocomposites materials are made of Nanocrystalline CEL and fibrin with periodate oxidation of the CEL. Fibrin chemical binding to the CEL can be mediated and adjusted, and are advantageous for small-diameter replacement vascular grafts (SDRVGs). The elastic hydrogel becomes stiffer thanks to the nanocrystalline CEL. Unexpectedly, the composites' maximum strength and elongation matched those of regular blood vessels [40]. Likewise, CEL acetate propionate and CEL nanowhiskers can be combined to create a composite material that can replace conventional synthetic blood vessels. The hydrogel matrix is provided by CEL acetate propionate, and nanowhiskers serve as fiber reinforcement. The percolated structure's improved mechanical qualities allow it to support surface physical stress showcases of human vasculature [41].

Being a quasi-water-soluble polymer with a glucose linkage, hydroxyethyl CEL is an excellent candidate for biomedical use. Increased cell viability and markedly accelerated cell growth are both benefits of hydroxyethyl CEL [42]. Additionally, it noticeably accelerates cell proliferation at high hydroxyethyl CEL concentrations [43].

Nanocrystalline CEL might be an effective medium for cell proliferation and attachment owing to its superior biocompatibility and mechanical attributes. The notable benefit of using nano-crystalline CEL is the fiber's large aspect ratio basic

building block, that further creates a natural fiber network of fibrils and otherwise, nanorods linked by mechanical incoherence and h-bonding. A network like this could be mechanically strengthened through cross-linking the individual nanofibers. On nano-CEL biomaterials like electrospun nanofibers, hydrogels, composites, membranes, and sponges, numerous cellular species have been grown [44]. The most preferred source of nano-CEL for cell culture is reportedly bacterial nano-CEL due to its biodegradability, non-toxicity, and highly porous structure [45]. Because it must coincide with the time at which tissue generates assures that the wounded tissue has been supplanted by normal tissues, and its mechanism has been revived, the frequency of graft degradation underneath a particular criterion is typically a major factor. Through the use of novel treatments that preserve hydration, those who actively engage in wound safeguarding and extracellular matrix regeneration, and are used in modern approaches to wound healing, such strategies have drawn a lot of attention in recent years [46]. A set of characteristics that will facilitate in excellent skin restoration ought to be prevalent in the materials used to fabricate newer wound dressings. Due to its advantageous traits, including biocompatibility, good mechanical capacity, non-toxicity, and significant moisture content, CEL is an appealing material for innovative wound closure. Numerous strategies can be employed to reconfigure CEL to achieve better its biocompatibility, uptake capacity and discharge, and anti-microbial activity at all levels of its internal structure while tackling the drawbacks of the starting source [46].

3.1.1 Bacterial CEL for Wound Dressing

Gram-negative bacteria strains produce a high yield of bacterial CEL (BC), often referred to as microbial CEL (MC), a cheap polysaccharide biopolymer with linear -1, 4-glucan chains. With only slight changes in its chemical and physical properties, such as a higher level of polymerization in BC than plant-extracted CEL, this type of CEL has a structure that is extremely similar to that of plant-extracted CEL [32, 46, 47].

It is commonly acknowledged that the bacterial CEL (BC) that some microorganisms make is a multifunctional nano-biomaterial. It is made up of linear glucan molecules that are joined together by hydrogen bonds and resemble plant CEL in appearance. However, when compared to other traditional natural or manufactured alternatives, BC performs better due to its specific superior chemical purity, crystallinity, biocompatibility, and ultrafine network architecture in sectors including biomedicine, water treatment, nano-fillers, functional devices, etc. New features are produced when BC is incorporated into a substance or employed as a scaffold and are connected to the intrinsic properties of BC [32].

With an average fiber diameter of 20–100 nm, BC has a much lower fiber diameter than plant-extracted CEL, resulting in a significantly higher accessible surface area. BC is formed of constructed microfibril bundles comprising hundreds of polyglucan chains [32, 46, 48]. A natural scaffold material for the regeneration of a range of tissues, BC, offers great water retention, high mechanical strength, and outstanding

biocompatibility thanks to its special nano-scaled three-dimensional network-like structure [49–52].

Their capacity to absorb exudates both during the application of the dressing and after their removal from the wound surface after healing is a crucial quality for the majority of repair materials. Materials used to heal skin tissue have often been porous, absorbent materials. Gauze, a common type of dressing, can stick to parched wound surfaces and cause trauma when it is removed. Due to its potential for use in cosmetics and medicine, interest in CEL generated by bacteria from surface cultures has steadily grown in recent years [53]. The commercialization of BC for wound care is quite promising when taking into account both the characteristics of BC and its clinical performance [49]. BC is utilized in many different industries and applications, but it is most frequently used in biomedical settings for things like cornea and bone scaffolds, vascular grafts, diagnostic equipment, and wound healing [47, 49, 52].

Microbial CEL (MC), which *Acetobacter xylinum* produces in massive quantities, has great potential as a cutting-edge wound healing therapy. The never-dried membrane's extraordinary mechanical strength and physical properties are due to its unusual nanostructure. In the marketing of MC for wound care products, it takes into account the properties, clinical efficacy, and development of the synthetic material. Effective and economical fermentation processes will be necessary, but they are not now available, in order to produce considerable volumes of the polymer [49].

A scaffold's biocompatibility is crucial to the success of tissue-engineered structures. *Acetobacter xylinum* produces CEL nano-fibrils that are 100 percent pure, which make up bacterial CEL. BC may be molded into three-dimensional structures and has a great mechanical strength. CEL-based products are thought to be biocompatible since they barely cause inflammatory or foreign body reactions. BC's in vivo biocompatibility has never been systematically assessed. Thus, it is essential to assess the in vivo biocompatibility while creating tissue-engineered constructs using a BC scaffold.

Rats received subcutaneous implants of BC for 1, 4, and 12 weeks. The implants were examined using histology, immunological histo-chemistry, and electron microscopy for signs of chronic inflammation, reactions to foreign bodies, cell proliferation, and angiogenesis. Inflammation around the implants was not visible. Additionally, there were no microscopic indicators of inflammation (i.e., a high number of small cells around the implants or the blood vessels). There were no large cells or fibrotic capsules. Fibroblasts invaded BC, which had been effectively assimilated into the host tissue, without causing any long-lasting inflammatory responses. The material has the potential to be employed as a scaffold in TENG because BC has outstanding biocompatibility [54]. BC is one of the most sought-after biomaterials for a variety of biomedical applications due to its distinctive features [54, 55].

One of the most prevalent types of biomass found in nature is CEL, which is also used as the primary feedstock in the paper and pulp industries. Fibers made of CEL can break with strength of up to 1 GN/m^2 (10,000 MPa). In addition to being traditionally derived from plant tissue (trees, cotton, etc.), CEL can also be created via fermentation with specific bacterial species in the form of nanofibers, producing

a very pure CEL product with special qualities. Intense research is being done on the production of microbial CEL and its uses. Bacterial CEL differs from CEL derived from plants in that it has particular physical characteristics. With a fiber diameter ranging from 20 to 100 nm, it has a fiber with a high aspect ratio. It has an extremely high surface area/unit mass as a result. This characteristic, along with the material's extreme hydrophilicity, results in an extremely high liquid loading capacity. This natural and biocompatible nanofiber is a smart choice for a variety of applications in many different industries, particularly those related to biomedical and biotechnology because of its distinctive qualities [55].

High effective surface area, a hydrophilic nature that provides BC a high liquid loading capacity, non-toxicity, biocompatibility, and plentiful supplies are among the qualities that make BC a highly adaptable biomaterial. Its natural structure also closely resembles a number of biological tissue characteristics, and it has the capacity to control cell adhesion as well as a high level of antigen immobilization for biosensor applications [46, 48, 56, 57]. There is also no use of harsh chemicals during BC manufacture, which further reduces the possibility of any deadly impurities remaining [57].

Since it can provide mechanical stability and flexibility, promote cell proliferation, retain liquids associated with wounds, allow gas exchange due to high porosity and permeability, and control wound exudates, BC offers enormous potential for wound-dressing applications and has been one of the top choices for wound-dressing biomaterials in recent years. Additionally, it does not trigger any unfavorable inflammatory responses from the host tissue [48, 54]. Another crucial feature of BC is its capacity for drug loading and controlled release, which is utilized in various scaffolds and dressings made of BC [58, 59].

In spite of these benefits and the availability of numerous commercial BC-based wound dressings, including Membracell®, BC exhibits minimal action against bacterial infections and has a highly rapid drug release profile due to its greater-than-ideal biodegradability. Although it is a relatively biocompatible material, it has been demonstrated that its cell and tissue biocompatibilities still need to be improved in a variety of wound-healing applications [47, 57, 60]. Surface alterations, immobilization of cell adhesion molecules like RGD molecules, and mixing with other biomaterials to create nano-composite materials are the main methods used to get around these problems [46, 47]. Other CEL derivatives, BC nanofiber production, and hydrogel creation are the key fabrication processes for wound-dressing applications, which will be covered. Anti-microbial components, such as anti-microbial medicines, have also been addressed [48, 61–64].

Being a natural polymer, CEL has a lot of potential as a dressing for wounds since it promotes granulation and epithelialization [65]. The creation of wound healing coverings for various wound types (such as burns and chronic wounds) and the customization of therapies for various wound healing stages are the current developments in wound care research. In this context, the creation of sophisticated nano-therapeutic materials is emphasized as a potentially effective method for managing particular stages of the healing process. Here, the effectiveness of Ca^{2+}-cross-linked nano-fibrillated CEL (NFC) hydrogels as dressings for wound healing is examined.

In vitro biocompatibility studies were carried out to investigate how the NFC hydrogels interacted with cellular functions closely associated with wound healing. The potential of the Ca^{2+}-cross-linked NFC hydrogels to repair wounds was also investigated using an in vivo dermo-epidermic full-thickness wound healing model in rats. The NFC hydrogels were able to sustain the proliferation of fibroblasts and keratinocytes, according to the in vitro tests. Additionally, it was suggested that the hydrogels might cause keratinocyte differentiation to occur. In vivo, the NFC hydrogels promoted healing without having any negative local tissue impacts, possibly as a result of their moisture-donating qualities and the Ca^{2+}-cross-helpful linker's influence on epidermal formation, which is detailed in this article. As a result, this work provides a thorough demonstration of the NFC hydrogels' capacity for wound healing and marks a significant advancement in the field's understanding and potential for improved wound healing applications [66].

A bioactive chemical is coated on a biopolymer-based material to create a bioactive wound dressing. To create a BC film for dressing application, papain was immobilized on bacterial CEL (BC) in the current work. At 25 °C and 150 RPM for 24 h, pure BC and BC that had been cross-linked with glutaraldehyde (BG) were immersed in papain solution. The appropriateness of BC loaded with papain membranes was evaluated using physical–chemical, morphological, loading/release, and antibacterial activities. Papain was successfully immobilized on BC fibrils, as shown by scanning electron microscopy/energy-dispersive X-ray spectroscopy and Fourier-transform infrared spectroscopy. The findings demonstrated that the amount of papain loaded onto the BC increased in the presence of glutaraldehyde and that the releasing ability of the BC membranes loaded with papain was active for at least 24 h. The papain addition reduced the CEL fiber's crystallinity (from 64 to 55%). Additionally, this caused the mechanical qualities of the membranes used for wound dressings to be cut in half compared to BC. BC/papain (BE) and BC/glutaraldehyde/papain (BEG) both had swelling ratios of 4546.7 554.9 and 4296.0 119.2%, respectively. The agar diffusion and cell growth inhibition test findings demonstrated the wound dressings antibacterial characteristics, totally inhibiting the growth of the tested strains of *Escherichia coli* (ATCC 25,922), *Pseudomonas aeuroginosa* (ATCC 27853), and *Staphylococcus aureus* (ATCC 25923). These results imply that the BC dressing created in this study is a promising substance for use in the biomedical industry [67].

The conventional cotton gauze made from CEL has long been used in clinical practice because wound dressing is crucial for wound healing. Cotton gauze does not have any active healing properties, though. In this work, a CEL sponge was made directly from a CEL solution in a NaOH/urea aqueous system with chilling, and subsequently, CEL/gelatin composite sponges were effectively manufactured by a cost- and environmentally-friendly method. The sponges' cytocompatibility and capacity for in vivo wound healing were assessed, and their structure and physical characteristics were described. The findings showed that the CEL sponge's presence of both macro- and micro-porous architecture efficiently improved wound healing when compared to cotton gauze. Additionally, basic fibroblast growth factor (bFGF) and gelatin were bound in the CEL sponge through hydrogen bonding in order to maintain their natural biocompatibility, resulting in outstanding mending efficacy.

In particular, the complete wound healing time for the wounds treated with bFGF-loaded CEL sponges was 7 days quicker than that for the wounds treated with gauze in the full-thickness cutaneous wound model. The CEL composite sponges' thin-walled pores were keys to producing highly efficient wound healing because they could meet the needs for oxygen permeability, regulated water vapor evaporation, and wound exudate absorption [68].

3.1.2 CEL-Based Hydrogels for Wound Dressing

Several hydrogels are designed from CEL, and its derivatives are used for wound dressing application.

For use as a wound dressing, carboxymethyl CEL-based hydrogels were created using a freeze–thaw technique and loaded with zinc oxide nanoparticles that had been heparinized. The loaded ZnO nanoparticles were reported to have an average particle size between 16 and 36 nm. After the addition of nanoparticles with lower pore densities, greater pore diameters were seen in SEM images. The heparinized nanoparticles from the hydrogels were first released in a burst, according to the in vitro drug release profile, and then, the drug was released over time. As more nanoparticles were placed into the hydrogel, the hydrogel's mechanical characteristics improved. The elongation at breakpoint reduced while the mechanical strength and Young's modulus increased. After two days, a cell viability analysis on hydrogels loaded with nanoparticles showed that they were not hazardous to HDF and L929 cells. After 24 h, the artificial wound generated during the wound healing assessment trials showed its ability to heal. A significant bactericidal efficacy of over 70% for ZnO-loaded hydrogels against *S. aureus* and *E. coli* was obtained when the antibacterial activity of the hydrogels was tested using the disk diffusion method [69].

Gupta et al. investigated the use of bacterial CEL hydrogels for wound dressings that were enclosed with curcumin. The hydrogels' water vapor transmission rate, which was measured in the range of 2526.32–3137.68 g/m^2/24 h, indicates that they can maintain a moist environment at the site of a wound. While conducting in vitro drug release experiments of curcumin from the hydrogels, it was discovered that 76.99 $\pm$ 4.46% of the loaded drug was released after 6 h, followed by a slow and sustained drug release mechanism. The hydrogels' high bioavailability of the medicine at the wound site made it possible to effectively manage bacterial-related infection. The oxidative stress at the wound site was decreased by the curcumin-loaded hydrogels [70].

Fan and colleagues developed and tested pH-sensitive drug-loaded CEL-based hydrogels as potential wound dressings. Hydrogels decomposed in somewhat acidic circumstances, according to an in vitro examination of deterioration, and the loaded medicines were liberated. The hydrogels' in vivo wound healing evaluation revealed that the weight of the rats was maintained throughout the wound healing process, indicating that the rats were in good health. These hydrogels also demonstrated a high rate of wound closure [71].

Hydrogels made of gelatin, diosgenin, and nano-CEL were created, and they were well suited for cell proliferation and adhesion based on their shape, which showed good porosity. The hydrogels' gel output varied from 83.67 ± 2.18% to 90.17 ± 3.51%. The hydrogels that were created had good water uptake efficiency and swelled to equilibrium in just one day. The hydrogels' mechanical characteristics revealed compression moduli with good strength, ranging from 3.04 ± 0.15 kPa to 8.04 ± 0.31 kPa. These hydrogels were identified as appropriate scaffolds for use in wound healing based on the results of their mechanical properties. When the in vitro antibacterial assessment of neomycin-loaded hydrogels was carried out, it was shown that *S. aureus* was more effectively inhibited than *E. coli* [72].

By carefully regulating the expression of colanic acid synthesis genes, bacterial CEL hydrogels from *Enterobacter sp. FY-07* were created with customized crystallinity. These hydrogels had a high water-holding capacity of 25,643% and good stability, low immunogenicity, purity, tensile strength, porosity, and biocompatibility characteristics. These characteristics are crucial for dressings used in wound care [73].

For the purpose of speeding up wound healing, oxidized CEL nanofiber-PVA hydrogels containing curcumin were created and described. While being examined with a microscope, the hydrogels revealed linked pores. The hydrogels' viscosity was shown to be dependent on the concentration of polyvinyl alcohol, and curcumin addition resulted in a decrease in viscosity. Over 100% of the L929 cells in the hydrogels' cell viability analysis utilizing the MTT assay demonstrated increasing cell viability over time in the investigation of these cells' proliferation (from day 1 to 7). The hydrogels containing 7.5% and 10% polyvinyl alcohol at pH 7.4 phosphate buffer saline solution had an in vitro drug release profile that demonstrated a sustained release of curcumin. When compared to 8.3 ± 1.13% of the control, the wound healing analysis showed a considerable wound closure between 28.8 ± 1.3% and 29.9 ± 1.7% [74].

Alginate was added to bacterial CEL-based hydrogels to enhance their effectiveness for managing wounds. These hydrogels showed improved water-retention capabilities. Additionally, it was determined that these scaffolds were biocompatible and practical for the treatment of bacterially infected wounds [75].

Dialdehyde carboxymethyl CEL was cross-linked with collagen to create biocompatible and stable hydrogel composites. Because the -amino group on collagen is ideal for covalent cross-linking with aldehyde groups of dialdehyde carboxymethyl CEL, the high collagen concentration in these hydrogels encouraged the high degree of cross-linking. The hydrogel's strong elastic behavior was strongly influenced by its high cross-linking capacity. More covalent connections were formed, increasing the hydrogel's durability and improving its resistance to enzyme degradation, viscoelastic characteristics, and heat stability. Dialdehyde carboxymethyl CEL hydrogels cross-linked with collagen did not stimulate any harmful cellular reactions, according to cell viability investigations on L929 fibroblasts utilizing CCK-8 assays [76].

Hydrogels made from bacterial CEL were developed and tested for managing wounds. It was made by mixing CEL with either *Jacaranda caroba* or *Calendula*

officinalis. In addition to promoting quick tissue regeneration, reducing severe inflammation, and not harming granulation, the hydrogel also offered a humid environment. Over the course of 7 days, the hydrogels demonstrated quicker re-epithelialization. The hydrogel's network of linked holes encouraged fast re-epithelialization and cell migration. The hydrogels were excellent for dry wounds and can lessen pain because of their permeability to metabolites and lowered temperature of the wound bed [77].

Liu and colleagues developed freeze–thaw cycle-based CEL nano-crystal reinforced nano-composite hydrogels with self-healing capabilities for wound healing. The hydrogels' porous morphology was visible in the SEM pictures, and as the PVA content was raised, the hydrogels' pore size shrank. The compressive stress of the hydrogels was shown to range between 95 and 1056 kPa in the mechanical properties investigation, with improved elasticity. In addition, when the amount of PVA grew, the hydrogels' Young's modulus and tensile stress increased from 0.52 to 9.9 MPa and 17 to 33 kPa, respectively. These findings demonstrated that PVA can enhance the mechanical qualities of CEL. By increasing the amount of PVA, the hydrogels' self-healing effectiveness was improved, and 3 g PVA content elevated the hydrogels' healing effectiveness to 37.03% [78].

Bacterial CEL hydrogels with thymol were developed and tested for the treatment of burn wounds. Due to the hydrophobic nature of thymol, the hydrogel water vapor transmission rate marginally decreased after thymol was loaded into the polymer matrix. The hydrogels supported the growth of mouse 3T3 fibroblast cells, displaying low cytotoxicity and enhanced cell viability, according to in vitro biocompatibility tests using the MTT assay. When compared to the common antibiotic, gentamycin, thymol-incorporated hydrogels had an excellent zone of inhibition in both Gram-positive and Gram-negative bacteria strains, particularly in the case of *S. aureus* and *K. pneumonia.* Studies on the hydrogels' effects on burn wound healing in female Wister rats showed that the wound grew larger by the fifth day. The burn wound area was drastically shrunk by 55% by day 15. On day 20, the wounds that had been treated with thymol-loaded CEL hydrogels and conventional CEL hydrogels had shrunk by 74.5% and 90.7%, respectively [79].

Hydrogels made of human hair keratin and carboxymethyl CEL allow for the controlled release of clindamycin. The water vapor transmission rate of the hydrogels was decreased by more keratin from 3200 g/m^2 to 1921 g/m^2/day, which is acceptable for wound treatment. Clindamycin was released from hydrogels in an initial burst over the course of the first 4 h, followed by a continuous release profile, according to the in vitro drug release mechanism under physiological settings. After 7 days of incubation in phosphate-buffered saline solution, the total amount of released clindamycin was 91.5 3.1%; keratin was added to reduce this amount. The hydrophilicity with rising keratin and declining water uptake value may be the cause of this. These findings imply that the drug delivery system's water absorption has an impact on the release kinetics of clindamycin. Due to the delayed release of the antibiotic, the hydrogel's in vitro antibacterial activity against *S. aureus* was 99.66%, and the addition of keratin decreased this figure [80].

Deng and colleagues created hydrogel using CEL and fenugreek gum. A porous structure with good thermal stability and water absorption was visible in the

composite hydrogel. The hydrogel's prolonged release mechanism was important. Additionally, the hydrogel showed excellent biocompatibility and non-toxic characteristics. The hydrogels enhance neovascularization and tissue restoration while reducing blood loss and hastening wound closure [81].

Mohamad and his colleagues revealed the use of bacterial CEL/acrylic acid hydrogel loaded with human epidermal keratinocytes and human dermal fibroblasts for the treatment of burn wounds. This in vivo experiment with athymic mice demonstrated that the hydrogel infused with cells sped up the healing of burn wounds. When compared to the control, which had a wound reduction of $64.79 \pm 6.84\%$ on day 13, the hydrogel had a wound reduction of $77.34 \pm 6.21\%$. In the mice given the hydrogel formulation, a high collagen deposition was seen, indicating their potential for use as a wound dressing [82].

Gupta and his colleagues created silver nanoparticles by combining curcumin with hydroxyl propyl cyclodextrin and then loading them into bacterial CEL hydrogel. The hydrogels offered a moist environment with excellent cytocompatibility, and they were successful in preventing the growth of microorganisms that cause wound infections, including *Candida auris*, *Staphylococcus aureus,* and *Pseudomonas aeruginosa* [83].

A single-center clinical investigation comparing a polylactide-based copolymer dressing to a nano-fibrillar CEL wound dressing (FibDex® by UPM-Kymmene Corporation) was described. For the study, 24 patients who needed skin grafts were enrolled. With the use of nano-fibrillar CEL wound dressing, skin elasticity was increased. When assessed for the management of skin graft donor sites, the CEL wound dressing was performed on par with polylactide. It did not need to be changed and was self-detachable. Pain was also lessened [84].

A hydrogel made of CEL and flaxseed gum was created to treat bleeding wounds. The hydrogel has a high degree of heat stability and had a 200% moisture absorption capacity. The biocompatible drug adsorption was 7.27 ± 0.15 mg/g, and it facilitated hemostasis and wound healing [85].

A biocompatible polyelectrolyte hydrogel patch made of gelatin and bacterial CEL from the *Gluconacetobacter xylinus* (MTCC7795) bacterial strain has the ability to repair on its own. The hydrogel's ability to self-heal was improved by bacterial CEL. Curcumin was added to the hydrogel, which improved its capacity for wound healing. With a zone of inhibition value of 15 ± 0.5 mm and 19 ± 1.0 mm against *E. coli* and *S. aureus*, respectively, the curcumin-loaded hydrogel inhibited bacterial growth. The release of curcumin from the hydrogel was regulated, and the presence of curcumin sped up cell division [86].

For high uptake of bioactive substances (resveratrol, dexpanthenol, allantoin, and linezolid), CEL hydrogel conjugated with carbon nanotubes was synthesized and assessed. In vivo wound healing was hastened. Linezolid had a sustained release and the ability to keep the antibiotic from deteriorating. With 95% cell survival, the hydrogel showed good biocompatibility with L929 mouse connective tissue fibroblasts [87].

A CEL hydrogel made of poly(vinyl alcohol)-2,3-dialdehyde was developed for use in bandages for wounds. The hydrogels had special qualities like high

porosity, high drug-loading capacity, and superior mechanical properties that made them manageable. They also had good adhesion to the skin, demonstrating biocompatibility and non-cytotoxicity [88].

Wang and coworkers reported using quaternized hydroxyethyl CEL/mesocellular silica hydrogel by one-pot radical graft co-polymerization to treat bleeding wounds. The mesocellular silica foam-loaded hydrogel (9.82 w/w%) activated the blood coagulation factors. Additionally, it decreased the in vitro plasma clotting time to 59%, resulting in less blood loss. Additionally, it improved in vivo wound healing in a full-thickness skin defect model [89].

Green deoxidizer mango peel extracts were used to create a carboxymethyl CEL/K-carrageenan/graphene oxide/konjac glucomannan hydrogel that was loaded with silver nanoparticles. The hydrogel showed strong antibacterial activity, was biocompatible, and sped up wound healing by promoting the growth of fibroblasts and hasty epithelialization [90].

A hydrogel and never-dried bacterial CEL fibers are used to make hydrogel-bacterial CEL nano-composite materials. These substances are appropriate for a variety of soft tissue replacement applications. Medical devices made from such composite materials can also be designed with controlled release of bioactive agent features [91].

The most of the aforementioned characteristics hold great promise for wound healing applications.

3.1.3 Bacterial CEL for Wound Dressing

Gram-negative bacteria strains produce a high yield of bacterial CEL (BC), often referred to as microbial CEL (MC), a cheap polysaccharide biopolymer with linear -1, 4-glucan chains. With only slight changes in its chemical and physical properties, such as a higher level of polymerization in BC than plant-extracted CEL, this type of CEL has a structure that is extremely similar to that of plant-extracted CEL [32, 46, 47].

It is commonly acknowledged that the bacterial CEL (BC) that some microorganisms make is a multifunctional nano-biomaterial. It is made up of linear glucan molecules that are joined together by hydrogen bonds and resemble plant CEL in appearance. However, when compared to other traditional natural or manufactured alternatives, BC performs better due to its specific superior chemical purity, crystallinity, biocompatibility, and ultrafine network architecture in sectors including biomedicine, water treatment, nano-fillers, functional devices, etc. New features are produced when BC is incorporated into a substance or employed as a scaffold and are connected to the intrinsic properties of BC [32].

With an average fiber diameter of 20–100 nm, BC has a much lower fiber diameter than plant-extracted CEL, resulting in a significantly higher accessible surface area. BC is formed of constructed microfibril bundles comprising hundreds of polyglucan chains [32, 46, 48]. A natural scaffold material for the regeneration of a range of tissues, BC, offers great water retention, high mechanical strength, and outstanding

biocompatibility thanks to its special nano-scaled three-dimensional network-like structure [49–52].

Their capacity to absorb exudates both during the application of the dressing and after their removal from the wound surface after healing is a crucial quality for the majority of repair materials. Materials used to heal skin tissue have often been porous, absorbent materials. Gauze, a common type of dressing, can stick to parched wound surfaces and cause trauma when it is removed. Due to its potential for use in cosmetics and medicine, interest in CEL generated by bacteria from surface cultures has steadily grown in recent years [53]. The commercialization of BC for wound care is quite promising when taking into account both the characteristics of BC and its clinical performance [49]. BC is utilized in many different industries and applications, but it is most frequently used in biomedical settings for things like cornea and bone scaffolds, vascular grafts, diagnostic equipment, and wound healing [47, 49, 52].

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For use as a wound dressing, carboxymethyl CEL-based hydrogels were created using a freeze–thaw technique and loaded with zinc oxide nanoparticles that had been heparinized. The loaded ZnO nanoparticles were reported to have an average particle size between 16 and 36 nm. After the addition of nanoparticles with lower pore densities, greater pore diameters were seen in SEM images. The heparinized nanoparticles from the hydrogels were first released in a burst, according to the in vitro drug release profile, and then, the drug was released over time. As more nanoparticles were placed into the hydrogel, the hydrogel's mechanical characteristics improved. The elongation at breakpoint reduced while the mechanical strength and Young's modulus increased. After two days, a cell viability analysis on hydrogels loaded with nanoparticles showed that they were not hazardous to HDF and L929 cells. After 24 h, the artificial wound generated during the wound healing assessment trials showed its ability to heal. A significant bactericidal efficacy of over 70% for ZnO-loaded hydrogels against *S. aureus* and *E. coli* was obtained when the antibacterial activity of the hydrogels was tested using the disk diffusion method [69].

Gupta et al. investigated the use of bacterial CEL hydrogels for wound dressings that were enclosed with curcumin. The hydrogels' water vapor transmission rate, which was measured in the range of 2526.32–3137.68 g/m^2/24 h, indicates that they can maintain a moist environment at the site of a wound. While conducting in vitro drug release experiments of curcumin from the hydrogels, it was discovered that 76.99 $\pm$ 4.46% of the loaded drug was released after 6 h, followed by a slow and sustained drug release mechanism. The hydrogels' high bioavailability of the medicine at the wound site made it possible to effectively manage bacterial-related infection. The oxidative stress at the wound site was decreased by the curcumin-loaded hydrogels [70].

Fan and colleagues developed and tested pH-sensitive drug-loaded CEL-based hydrogels as potential wound dressings. Hydrogels decomposed in somewhat acidic circumstances, according to an in vitro examination of deterioration, and the loaded medicines were liberated. The hydrogels' in vivo wound healing evaluation revealed that the weight of the rats was maintained throughout the wound healing process, indicating that the rats were in good health. These hydrogels also demonstrated a high rate of wound closure [71].

Hydrogels made of gelatin, diosgenin, and nano-CEL were created, and they were well suited for cell proliferation and adhesion based on their shape, which showed good porosity. The hydrogels' gel output varied from 83.67 ± 2.18% to 90.17 ± 3.51%. The hydrogels that were created had good water uptake efficiency and swelled to equilibrium in just one day. The hydrogels' mechanical characteristics revealed compression moduli with good strength, ranging from 3.04 ± 0.15 kPa to 8.04 ± 0.31 kPa. These hydrogels were identified as appropriate scaffolds for use in wound healing based on the results of their mechanical properties. When the in vitro antibacterial assessment of neomycin-loaded hydrogels was carried out, it was shown that *S. aureus* was more effectively inhibited than *E. coli* [72].

By carefully regulating the expression of colanic acid synthesis genes, bacterial CEL hydrogels from *Enterobacter sp. FY-07* were created with customized crystallinity. These hydrogels had a high water-holding capacity of 25,643% and good stability, low immunogenicity, purity, tensile strength, porosity, and biocompatibility characteristics. These characteristics are crucial for dressings used in wound care [73].

For the purpose of speeding up wound healing, oxidized CEL nanofiber-PVA hydrogels containing curcumin were created and described. While being examined with a microscope, the hydrogels revealed linked pores. The hydrogels' viscosity was shown to be dependent on the concentration of polyvinyl alcohol, and curcumin addition resulted in a decrease in viscosity. Over 100% of the L929 cells in the hydrogels' cell viability analysis utilizing the MTT assay demonstrated increasing cell viability over time in the investigation of these cells' proliferation (from day 1 to 7). The hydrogels containing 7.5% and 10% polyvinyl alcohol at pH 7.4 phosphate buffer saline solution had an in vitro drug release profile that demonstrated a sustained release of curcumin. When compared to 8.3 ± 1.13% of the control, the wound healing analysis showed a considerable wound closure between 28.8 ± 1.3% and 29.9 ± 1.7% [74].

Alginate was added to bacterial CEL-based hydrogels to enhance their effectiveness for managing wounds. These hydrogels showed improved water-retention capabilities. Additionally, it was determined that these scaffolds were biocompatible and practical for the treatment of bacterially infected wounds [72].

Dialdehyde carboxymethyl CEL was cross-linked with collagen to create biocompatible and stable hydrogel composites. Because the -amino group on collagen is ideal for covalent cross-linking with aldehyde groups of dialdehyde carboxymethyl CEL, the high collagen concentration in these hydrogels encouraged the high degree of cross-linking. The hydrogel's strong elastic behavior was strongly influenced by its high cross-linking capacity. More covalent connections were formed, increasing the hydrogel's durability and improving its resistance to enzyme degradation, viscoelastic characteristics, and heat stability. Dialdehyde carboxymethyl CEL hydrogels cross-linked with collagen did not stimulate any harmful cellular reactions, according to cell viability investigations on L929 fibroblasts utilizing CCK-8 assays [76].

Hydrogels made from bacterial CEL were developed and tested for managing wounds. It was made by mixing CEL with either *Jacaranda caroba* or *Calendula*

officinalis. In addition to promoting quick tissue regeneration, reducing severe inflammation, and not harming granulation, the hydrogel also offered a humid environment. Over the course of 7 days, the hydrogels demonstrated quicker re-epithelialization. The hydrogel's network of linked holes encouraged fast re-epithelialization and cell migration. The hydrogels were excellent for dry wounds and can lessen pain because of their permeability to metabolites and lowered temperature of the wound bed [77].

Liu and colleagues developed freeze–thaw cycle-based CEL nano-crystal reinforced nano-composite hydrogels with self-healing capabilities for wound healing. The hydrogels' porous morphology was visible in the SEM pictures, and as the PVA content was raised, the hydrogels' pore size shrank. The compressive stress of the hydrogels was shown to range between 95 and 1056 kPa in the mechanical properties investigation, with improved elasticity. In addition, when the amount of PVA grew, the hydrogels' Young's modulus and tensile stress increased from 0.52 to 9.9 MPa and 17 to 33 kPa, respectively. These findings demonstrated that PVA can enhance the mechanical qualities of CEL. By increasing the amount of PVA, the hydrogels' self-healing effectiveness was improved, and 3 g PVA content elevated the hydrogels' healing effectiveness to 37.03% [78].

Bacterial CEL hydrogels with thymol were developed and tested for the treatment of burn wounds. Due to the hydrophobic nature of thymol, the hydrogel water vapor transmission rate marginally decreased after thymol was loaded into the polymer matrix. The hydrogels supported the growth of mouse 3T3 fibroblast cells, displaying low cytotoxicity and enhanced cell viability, according to in vitro biocompatibility tests using the MTT assay. When compared to the common antibiotic, gentamycin, thymol-incorporated hydrogels had an excellent zone of inhibition in both Gram-positive and Gram-negative bacteria strains, particularly in the case of *S. aureus* and *K. pneumonia.* Studies on the hydrogels' effects on burn wound healing in female Wister rats showed that the wound grew larger by the fifth day. The burn wound area was drastically shrunk by 55% by day 15. On day 20, the wounds that had been treated with thymol-loaded CEL hydrogels and conventional CEL hydrogels had shrunk by 74.5% and 90.7%, respectively [79].

Hydrogels made of human hair keratin and carboxymethyl CEL allow for the controlled release of clindamycin. The water vapor transmission rate of the hydrogels was decreased by more keratin from 3200 g/m^2 to 1921 g/m^2/day, which is acceptable for wound treatment. Clindamycin was released from hydrogels in an initial burst over the course of the first 4 h, followed by a continuous release profile, according to the in vitro drug release mechanism under physiological settings. After 7 days of incubation in phosphate-buffered saline solution, the total amount of released clindamycin was 91.5 3.1%; keratin was added to reduce this amount. The hydrophilicity with rising keratin and declining water uptake value may be the cause of this. These findings imply that the drug delivery system's water absorption has an impact on the release kinetics of clindamycin. Due to the delayed release of the antibiotic, the hydrogel's in vitro antibacterial activity against *S. aureus* was 99.66%, and the addition of keratin decreased this figure [80].

Deng and colleagues created hydrogel using CEL and fenugreek gum. A porous structure with good thermal stability and water absorption was visible in the

composite hydrogel. The hydrogel's prolonged release mechanism was important. Additionally, the hydrogel showed excellent biocompatibility and non-toxic characteristics. The hydrogels enhance neovascularization and tissue restoration while reducing blood loss and hastening wound closure [81].

Mohamad and his colleagues revealed the use of bacterial CEL/acrylic acid hydrogel loaded with human epidermal keratinocytes and human dermal fibroblasts for the treatment of burn wounds. This in vivo experiment with athymic mice demonstrated that the hydrogel infused with cells sped up the healing of burn wounds. When compared to the control, which had a wound reduction of $64.79 \pm 6.84\%$ on day 13, the hydrogel had a wound reduction of $77.34 \pm 6.21\%$. In the mice given the hydrogel formulation, a high collagen deposition was seen, indicating their potential for use as a wound dressing [82].

Gupta and his colleagues created silver nanoparticles by combining curcumin with hydroxyl propyl cyclodextrin and then loading them into bacterial CEL hydrogel. The hydrogels offered a moist environment with excellent cytocompatibility, and they were successful in preventing the growth of microorganisms that cause wound infections, including *Candida auris*, *Staphylococcus aureus,* and *Pseudomonas aeruginosa* [83].

A single-center clinical investigation comparing a polylactide-based copolymer dressing to a nano-fibrillar CEL wound dressing (FibDex® by UPM-Kymmene Corporation) was described. For the study, 24 patients who needed skin grafts were enrolled. With the use of nano-fibrillar CEL wound dressing, skin elasticity was increased. When assessed for the management of skin graft donor sites, the CEL wound dressing was performed on par with polylactide. It did not need to be changed and was self-detachable. Pain was also lessened [84].

A hydrogel made of CEL and flaxseed gum was created to treat bleeding wounds. The hydrogel has a high degree of heat stability and had a 200% moisture absorption capacity. The biocompatible drug adsorption was 7.27 ± 0.15 mg/g, and it facilitated hemostasis and wound healing [85].

A biocompatible polyelectrolyte hydrogel patch made of gelatin and bacterial CEL from the *Glucanoacetobacter xylinus* (MTCC7795) bacterial strain has the ability to repair on its own. The hydrogel's ability to self-heal was improved by bacterial CEL. Curcumin was added to the hydrogel, which improved its capacity for wound healing. With a zone of inhibition value of 15 ± 0.5 mm and 19 ± 1.0 mm against *E. coli* and *S. aureus*, respectively, the curcumin-loaded hydrogel inhibited bacterial growth. The release of curcumin from the hydrogel was regulated, and the presence of curcumin sped up cell division [86].

For high uptake of bioactive substances (resveratrol, dexpanthenol, allantoin, and linezolid), CEL hydrogel conjugated with carbon nanotubes was synthesized and assessed. In vivo wound healing was hastened. Linezolid had a sustained release and the ability to keep the antibiotic from deteriorating. With 95% cell survival, the hydrogel showed good biocompatibility with L929 mouse connective tissue fibroblasts [87].

A CEL hydrogel made of poly(vinyl alcohol)-2,3-dialdehyde was developed for use in bandages for wounds. The hydrogels had special qualities like high

porosity, high drug-loading capacity, and superior mechanical properties that made them manageable. They also had good adhesion to the skin, demonstrating biocompatibility and non-cytotoxicity [88].

Wang and coworkers reported using quaternized hydroxyethyl CEL/mesocellular silica hydrogel by one-pot radical graft co-polymerization to treat bleeding wounds. The mesocellular silica foam-loaded hydrogel (9.82 w/w %) activated the blood coagulation factors. Additionally, it decreased the in vitro plasma clotting time to 59%, resulting in less blood loss. Additionally, it improved in vivo wound healing in a full-thickness skin defect model [89].

Green deoxidizer mango peel extracts were used to create a carboxymethyl CEL/K-carrageenan/graphene oxide/konjac glucomannan hydrogel that was loaded with silver nanoparticles. The hydrogel showed strong antibacterial activity, was biocompatible, and sped up wound healing by promoting the growth of fibroblasts and hasty epithelialization [90].

A hydrogel and never-dried bacterial CEL fibers are used to make hydrogel-bacterial CEL nano-composite materials. These substances are appropriate for a variety of soft tissue replacement applications. Medical devices made from such composite materials can also be designed with controlled release of bioactive agent features [91].

Most of the aforementioned characteristics hold great promise for wound healing applications.

3.2 Application of CEL in Drug Delivery System

In terms of delivery aids, excipients, and technology that allows for quick or gradual drug release, drug delivery is quite inventive. Analgesics, which frequently require five or six pills per day, can, for instance, be lowered to a single dose by utilizing the proper excipients, which are based on carbohydrate polymers. The most fundamental categories for categorizing polymers are natural and synthetic polymers, which are used in pharmaceuticals.

The hierarchical evolution of the contemporary delivery of drug started with the use of polymer carriers to induce the spatiotemporal release of medications in implanted reservoir systems as well as pulsatile drug delivery system. Although traditional drug delivery formulations have made significant contributions to illness treatment, the development of potent and specific biological therapies has increased the demand of latest technology such as intelligent delivery systems. When developing new drug delivery systems, Heller [92] and Langer and Peppas [93] underlined the significance of chemical engineering innovation and suggested that feedback control be made available as a standard feature. Significant findings have been obtained from the investigation solvent-activated as well as diffusion-controlled formulations for drug delivery system. Pharmaceutical drugs have been attached to polymers to change the circulation as well as transport of drug to enable active and passive targeting. Finally, polymeric-based drug delivery research has resulted in recognition systems

and polymer carriers that promote cytoplasmic delivery of new therapies [94]. Bio-based materials are gaining traction in biomedical disciplines such as TENG, wound healing, and medication delivery, contributing to an increase in demand. Polysaccharides, which are long-chain biopolymeric carbohydrate molecules largely made up of monosaccharide units, are bio-based materials with enormous promise in biomedical applications and the distinct advantages of natural polymers over synthetic polymers. Based on their widespread distribution in nature, CEL and chitin are the most important natural biopolymers among the various types of polysaccharides. CEL is typically made by plants and trees, whereas chitin is made by lower animals [2, 95].

A drug delivery system is described as a delivery of medications in a predetermined amount to particularly specified organs at a predetermined time interval. Drug delivery systems distribute medications to specific cells, tissues, and organs with the transfer mechanism being able to respond to stimuli like pH, temperature, and light along with electric and magnetic fields. CEL has a long history of use in the pharmaceutical business, where it has been combined with various excipients and utilized as a tablet coating for oral delivery [96, 97]. Cellulosic materials should have regulated diffusive characteristics and dissolvability as a drug delivery system. For example, CEL and its derivatives have been shown to have definite drug delivery patterns in oral dosage forms via rapid, regulated, or delayed release [98, 99]. Furthermore, cellulosic materials' intrinsic resistance to the acidic environment of the stomach makes them ideal for use as enteric coatings on capsules or tablets [100]. In compounded pharmaceuticals, powdered CEL and MCC are utilized as adsorbents, capsule diluents, and thickening stabilizing agents [101]. MCC has visco-elastic properties and is sensitive to strain rate. Because the period for plastic deformation is limited in high-speed tableting, elastic effects are more prominent [102]. As a result, the dependence of MCC on the strain rate should be taken into account while formulating and dosing [103]. One of the most popular hydrophilic biodegradable polymers, hydroxypropyl methyl CEL has been approved by the UDFDA for use in controlled-release formulations (FDA) [104]. Injectable glycerophosphate thermosensitive solutions with vancomycin-embedded hydroxy propyl methyl CEL microparticles are created for the local treatment of osteomyelitis [105]. The porous and spongy nature of hydroxypropyl methyl CEL hydrogels permits a long-term release profile in vitro, indicating they have a lot of potential for use in long-term antibiotic delivery [105].

3.2.1 Applications of CEL-Based Materials in Sustained Drug Delivery Systems

Formulation scientists investigated the use of biodegradable polymer as well as natural-based sustained-release systems for pharmaceuticals to obtain the appropriate release profile. Hydrogels were first used in drug delivery applications in the 1960s. Hydrogel membranes based on poly methacrylates were used for dental caries by controlled release devices with fluorides.

The use of a natural CEL-based polymer to modify the surface of the NPS to improve their hydrophilic qualities is a new technique. The phagocytosis process

would be bypassed or delayed by covalent alteration of the drug NP surface, resulting in increased drug bioavailability in the systemic circulation to reach the target. Because of its great biocompatibility, biodegradability, and non-toxicity, CMC and HPMC have been employed in the creation of drug-based NPs [106].

Because of their steric forces, a variety of CEL derivatives provide protection. Unbound interactions with proteins or enzymes are prevented by the pressures. Because of their recognition and mucoadhesive qualities, this boosts the organ or specific tissue targeting [107].

CEL derivatives such as CEL triacetate, polycarbonate, and polypropylene can help build membrane structures. Transdermal medication therapy has been successfully administered using polyacrylates and a few CEL derivatives. Because of their good film-forming capabilities, CEL as well as acrylic polymers are commonly utilized in pharmaceutical coatings to help protect and sustain drug release. CEL and its derivatives are commonly utilized to change the release of drugs from solid dosage forms like capsules and tablets, as well as to aid in water retention, film formation, and adhesive qualities. The derivatives are also known for their ability to act as an emulsifying as well as suspending agents.

Hoang et al. (2017) developed self-assembled cabazitaxel NPs with 100 nm size attached with carboxy methyl CEL-based polymer, a clinically approved alternative to DTX (Cellax-CBZ). In mice with prostate cancer, Cellax-CBZ delivered around 157-fold more cabazitaxel to PC3-RES and was determined to be safe when administered at a 25-fold higher dose than free cabazitaxel. DTX-resistant mCRPC-based mouse models showed better tumor suppression in the study. Fortunately, Cellax-CBZ paved the way for a more effective mCRPC treatment than the currently available CBZ [108]. Chen et al. [33] designed a drug delivery device that can entrap both pH-responsive as well as hydrophobic drugs. Cyclodextrin polymer (-CDP) was used to entrap ibuprofen (IBU). Through physical means, the core shell was crossed and connected with sodium alginate (SA), sodium carboxy methyl CEL (CMC), and HEC, and the capsule improved IBU solubility and sustained release at a specific pH. This polysaccharide hydrogel capsule delivery technology may be useful in the manufacture of oral medication delivery [109, 110].

3.2.2 Role of CEL Derivative in Development of Novel Drug Delivery Systems

Novel Drug Delivery Systems (NDDS) are methods, formulations, technologies, and systems for safely delivering a pharmaceutical molecule in the body as required to produce its intended therapeutic effects. The NDDS is a drug delivery system that includes cutting-edge strategies in addition to conventional methods. The effectiveness of a medication can be significantly impacted by how it is given. While dosages outside of this range may be hazardous or have no therapeutic value at all, some drugs have an ideal concentration range within which they work best. Polymer science, pharmaceutics, and molecular biology are all combined in a novel drug delivery system (NDDS) [111–113].

Liu et al. (2017) developed a pH gradient-releasing pellet of Vinpocetine with Eudragit L30D55, HPMC and Eudragit FS30D by using extrusion spheronization technique. The dosage form was able to improve the approx. 149.8% oral bioavailability in comparison with commercial Vinpocetine tablets [114].

Rao et al. (2018) used biological amino-based compounds within graphene oxide to form an amino-fumed graphene complex, which then combined with CMC to form a graphene-CMC combination that works as a drug embossing carrier matrix. DOX was injected into graphene-CMC, resulting in the graphene-CMC/DOX system. The drug release was approximately 65.2% at pH 5. The cytotoxicity of cervical cancer cells like Hela cells and mouse fibroblasts (NIH-3T3 cells) was negative in a study [115]. Tania et al. (2017) developed and described solid support similar to sponges made by lyophilizing CEL derivative hydrogels. The CEL-based sponges were known for sticking to the vaginal cavity and being rehydrated by vaginal fluid interaction [116]. In order to create a floating tablet, Qi et al. (2015) compressed a hydrophilic polymer (HPC) and covered it with sodium bicarbonate to make it effervescent. The influence of drug, HPC (weight) and HPC viscosity on the drug release rate was primarily investigated. In the absence of pepsin, the average floating time was 30 s and continued up to 11–12 h in pH 1.2 fluid SGF (simulated gastric fluid), indicating zero-order drug release. Compared to TaiLiBiTuo®, ofloxacin's bioavailability after dosing was determined to be 172.20% in New Zealand rabbits. Overall, the floating tablet coated with HPC was found to be a promising gastroretentive delivery mechanism [117].

Colorectal cancer is said to be responsible for 50,000 deaths in the United States and 20,000 deaths in Italy. Males in their 50s and 60s had a higher death rate from colorectal cancer than females. Conventional chemotherapy based on oral drug administration is ineffective for its treatment because effective concentrations of the drug cannot reach the target site due to their disintegration and absorption in the stomach and small intestine [118]. To address this issue, the dose is typically raised to achieve effective concentration at the target site, although this has various negative consequences [119]. Development of drug delivery methods that can selectively target the colorectal region is required. Several cancer studies have documented the pain experienced by cancer patients who are ambulatory or undergoing anticancer medication. As a result, cancer patients' pain must also be managed.

Cross-linked polymers with a three-dimensional structure known as hydrogels have a hydrophilic property that enables them to absorb enormous amounts of water. These polymeric materials might be natural, synthetic, or a combination of both. Hydrogels have the potential to swell and provide moderate to high physical, chemical, and mechanical stability, making them ideal for their intended function. Natural or semi-synthetic polymers such as alginate or carboxymethyl CEL have been widely discussed in the literature for the construction of hydrogels [120]. Carboxymethyl CEL is a biodegradable, non-toxic, low-cost, renewable polymer made from either bacterial or plant CEL. It comprises carboxymethyl groups, which are formed when chloroacetate reacts with CEL in an alkali solution, resulting in glucose replacements at positions C_2, C_3, and C_6. Carboxymethyl CEL is hydrophilic and more sensitive to the hydrolytic activity of cellulases as a result of this substitution [121].

3.2.3 Application of CEL Derivatives in Oral Peptide and Protein-Based Drug Delivery

The advent of an oral dosage form that ensures optimal bioavailability of therapeutic proteins and peptides will undoubtedly change the way certain diseases are treated. As a result, various attempts to attain this goal have been attempted so far. Incorporating CEL derivates in the manufacture of oral formulations is one of these initiatives. The main rationale for including these chemicals is to defend against various gastrointestinal disorders [122].

It also gives excellent mucoadhesive qualities to the formulation. Polyacrylic acid or CEL derivatives make up the majority of bio-adhesive polymers on the market today [123]. Another example in the same setting is cross-linking chitosan nanoparticles with pH-sensitive polymer like HPMC phthalate, a. This chitosan nanoparticle-based insulin formulation displayed significant biological activity and stability in an acidic environment. Furthermore, the modified formulation containing hydroxypropyl methylCEL phthalate revealed a tenfold improvement in hypoglycemia impact when compared to oral insulin and insulin loaded in plain chitosan nanoparticles [124]. In the design of pulsatile drug delivery systems, CEL polymers are also used as additives (PDDS). A swellable inner layer of hydroxypropyl methylCEL, one of the system's several coating layers, increases the formulation's durability against proteolytic degradation and is intended to release insulin [125].

3.2.4 Application of CEL Derivatives in Oral and Dental Treatment

Plant and bacteria CEL have a lot of potential applications in the biological field, including the dentistry [126]. The CEL derivatives CMCNa and HEC were combined with gelatin to produce porous matrices of metronidazole for topically used in the periodontal pocket [127]. In order to create mucosal films for the precise distribution of allantoin to the mucosa, Lafleur et al. [128] combined a range of semi-synthetic CEL derivatives, including EC, HEC, HPMC, and CMC sodium salt. A three-layer HPC adhesion film with dibucaine (0.25 mg/cm^2) was developed and used by Yamamura et al. to treat mouth ulcers brought on by chemotherapy or radiotherapy [129].

In an investigation by Kohda et al., polymeric films containing 30% lidocaine and prepared using HPC and EC (1:1) showed improved buccal mucosa adhesion for 60–120 min in clinical evaluation in all subjects of the clinical trials [130]. Eschel et al. [131] used a variety of polymers to make hydrocortisone acetate mucoadhesive tablets for treating oral mucosal lesions, including HPMC, Carbopol 974P, and polycarbophil. Using a blend of HPC and carbomer, Kamel et al. developed bio-adhesive tablets that attached to the gingiva and offered a longer effect than the citrus oil put in them, which was used to treat aphthae [132]. Bansal et al. investigated the dissolution of satranidazole-loaded CMCNa-based mucosal gel, a periodontitis therapy. The drug's release from the carrier was positively controlled release for eight hours, in accordance with Fick's diffusion law [133].

4 Conclusion

Because of its outstanding biophysical properties, biodegradability, biocompatibility, and fewer cytotoxicity, CEL seems to have the potency to be used in biological implants and scaffolds for TENG, body-organ implants, wound and burn dressing materials, and pharmaceutical formulation. Surface modification and the kind of CEL used in biomedical applications, such as hydrogel, solid film, scaffold, membrane, and nanomaterials, offer a simple and efficient technique for adjusting how well biomaterials interact with living tissue. Because of their durability and compliance, exploratory study on cellulosic materials has demonstrated that they are preferable biomaterials in TENG compared to other biopolymers. Although the incorporation of CEL in technologies for repair and regeneration and wound healing has been established and exploited, further integrative research is necessary to advance such components. Potential uses of CEL as well as its variants in the pharmaceutical sector might include medication delivery systems and/or advanced artificial skin or WL procedures. More study is required to evaluate the possible pharmacological side effects and cytotoxicity profile of cellulosic materials, even if they are not harmful by nature. There are new opportunities for the creation of innovative functional materials due to different CEL surface and/or bulk modifications. Future research should concentrate on the impact of foreign molecule addition on the cytotoxicity and/or biocompatibility of nano-CEL as a consequence. Clearly, despite tremendous advances in biomedical nano-cellulosic materials, this field is still in its early stages. There are still multiple issues to be addressed and numerous avenues to pursue on this subject for future research work.

CEL can indeed be tweaked through its surface and/or bulk in innovative ways, opening up possibilities for the creation of novel delivery materials. Consequently, prospective research should concentrate on the way the incorporation of foreign molecules affects nano-CEL's cytotoxicity and/or biocompatibility. Apparently, despite significant advances in healthcare nanoscale cellulosic materials, this field is in its infancy. We feel that there continue to be various issues that must be addressed as well as several avenues to explore on this topic.

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Sustainable Biomedical Applications of Cellulose

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Abstract Cellulose present in plant cell wall and in some microbes is the most plentiful carbohydrate on earth. Due to its complex structure and biological-friendly nature, it can be widely used as such or in derived form in biological processes. Thin fiber of cellulose called cellulose nanofiber is used for many medicinal purposes. High specific surface area, reactive surface, and mechanical strength make cellulose biocompatible. The potency of biodegradability, nontoxic, and are relatively low cost makes cellulose a good choice for medical use. Nanofibers of cellulose can be used in controlled drug delivery, dressing material for wound healing, excipient, and in transdermal drug delivery, and as anticancer and antimicrobial agent. Cellulose nanofibers wound dressing revealed high biocompatibility and rapid epithelialization of burn wounds. Cellulose nanofibers as excipient enhance the stability of emulsion by viscosity modification and increasing the tensile strength of tablets. Anticancer drug-loaded hydrogels exhibited the highest drug release at pH 7 by using cellulose derivative. Blood vessel, nucleus pulposus replacement, enzyme immobilization, cardiac, ophthalmic, and neural tissue engineering is also presented. Application of microbial cellulose is also important which is used in wound healing and regeneration of damaged organs. Microbial cellulose membranes, having a unique nanostructure, could have many other uses in wound healing and regenerative medicine, such as guided tissue regeneration (GTR), periodontal treatments, or as a replacement for dura mater showing that it could eventually become an excellent platform technology for medicine. If microbial cellulose can be successfully mass produced, it will eventually become a vital biomaterial and will be used in the creation of a wide variety of medical devices and consumer products. The present chapter unveils current and potential uses of cellulose and its derivatives in biomedical sciences.

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1 Introduction

Cellulose is made up of glucose units ($C_6H_{10}O_5$) and also its a naturally occurring polymer. Natural biopolymers such as cellulose and chitin are the most important polysaccharides found in nature [76]. Low-ranking animals provide the chitin, whereas plants and wood are the primary sources of cellulose [8]. This chapter discusses the characteristics, manufacturing techniques, and cellulose derivatives in the biomedical sector, and applications of cellulose. Because of its excellent mechanical and physical properties, the use of cellulose and its derivatives has received considerable attention in biomedical applications. Cellulose, the utmost common organic material in the world, is produced by plants. Plant tissues and cells are made up mostly of this material. Cellulose is an important long-chain polymer in the human food chain. This polymer may be employed as an excipient in a broad variety of industries, including veterinary foods, wood, paper, textiles, and clothes [6, 76]. Cellulose naturally gains utility, high specific strength, and flexibility via its hierarchical structure. This material is also biodegradable, low density, and cost-efficient [26]. Porosity and interconnectivity may be tailored using cellulosic materials for biological purposes [107].

Derivatives of cellulose are used extensively in the cosmetic and pharmaceutical industries. Cellulose derivatives have two main families that are cellulose ethers and cellulose esters with different physical, mechanical, and chemical properties. It is common for these polymers to be used in the manufacturing of pharmaceuticals and healthcare products. They are used in osmotic drug administration, bioadhesion, and mucoadhesion, as compressibility enhancers used in compression tablets, as thickening agents and stabilizers used in liquid dosage and granules and tablets as binding agents in many pharmaceutical applications. Transdermal patch fillers, taste-masking agents, pressure-sensitive adhesives, and free-flowing agents have also been made using polymeric compounds. New derivatives and unique applications of already existing chemicals have been discovered by pharmaceutical researchers, making cellulose and cellulose-based polymers more and more prominent in the pharmaceutical industry.

Several recent developments in the use of cellulosic materials outside of paper and textile manufacture have been made including biomedical uses. Biomedical applications cellulosic materials have the potential to be cost-effective novel materials because of their biodegradability, biocompatibility, and low cytotoxicity. Cellulose, due to its chemical activity, may be transformed into useful products. Preventive medicine and health care have always relied heavily on cellulosic materials as a primary component.

The composition, cellulose chain packing, and aggregation vary across cellulose-producing organisms; its structure is complicated. Glucose residues from 1000 to 30,000 polymerize per glucose unit depending on the supply and treatment of cellulose. Each glucose residue has three hydroxyl groups [3]. Oxygen and hydroxyl groups of the following cellulose chain establish intrachain hydrogen bonds, which help to maintain unbranched conformation of cellulose molecules. The cellulose

molecules found in algae, the cell walls of plants, tunicate epidermal cell membranes, and bacteria form ordered parallel layers to form primary fibrils.

Different sources and techniques may be used to make cellulose, which can be both synthetic and nonsynthetic (natural). It may take many shapes and be used for many different things. Anti-caking ingredient for shredded cheese has been sought, as well as a peelable hot dog casing for processing aids in the food industry. Texturizer, emulsifier, extender, fat substitute, and bulking ingredient in low-calorie meals are all FDA-approved uses for cellulose in different forms. This ingredient, which was used as a filler in tablets, could be made from fibrous materials like wood or cotton and used in any food product that needed a pulp. Tablet diluent and binder microcrystalline cellulose is an improved and more practical type of cellulose powder used mostly in the pharmaceutical industry. The strong intramolecular and intermolecular hydrogen bonds that occur across various chains, cellulose, cannot be dissolved in water or most common solvents [38]. The low solubility of cellulose does not stop it from being used in an extensive range of products including netting, coatings, composites, and upholstery as well as packaging and paper. Chemical modifications are made to cellulose that may be tailored for specific industrial applications are also produce in order to increase cellulose derivatives (cellulosics) and processing capacity. Membranes for blood purification are one example of a cellulosic material used in biomedical applications since they are strong and reproducible while being recyclable (Table 1).

Table 1 Degree of polymerization of cellulose from various sources

Source	Type	Degree of polymerization (range)
Wood		
	Wood from various species	6000–10,000
	Wood pulp (in general)	2000–4000
	Wood CNF	250–3500
Plant		
	Cotton Corn Jute Bagasse Corn stover Corn kernel Wheat straw	10,000–15,000 1700 1900 1000 2500 1700 2600
Bacteria		7000–16,000
Algae		2500–4300
Tunicate		700–3500

1.1 Cellulose Sources

For the sake of categorization, there are five different types of cellulose, which include wood, plant, bacterium, and tunicate (Fig. 1). To date, WC and PC have overtaken BC, tunicate-based cellulose (BC), and algae-based cellulose and as the most widely used cellulose varieties because of their availability and cost, respectively.

2 Production of Bacterial Cellulose

Celluloses I and II are completely studied among the four allomorphic forms of K. xylinus' bacterial cellulose produced extracellular by fermentation of carbohydrates. For unknown reasons, these bacteria are known to produce extracellular polysaccharides, which congeal at the top of their growth medium and prevent them from drying out. This allows colonies of bacteria to grow close to the surface and keeps them from drying out [104]. It is necessary for the bacteria to initially passively accept a glucose supply from the environment before they can begin isomerizing glucose. To make uridine diphosphate glucose, the UTP isomer and this isomer must be mixed, converts UDP-glucose into linear 1, 4 glucan chains, by glucose synthase-A which are then activated by the cyclic di-GMP. Bacteria then excrete the cellulose chains via the cell wall pores. It will switch to fructose enzymatic pathways if there are no more glucose sources available to it [52]. BcsABCD (a specific operon found in K. xylinus in 1999) governs the metabolic activities of the organism [42]. A gene in the bcsA, bcsABCD operon, encodes the catalytic component of the enzyme cellulose synthase. Second gene, bcsB, produces a component on the cellulose synthase, which is very crucial since this interaction begins the production of cellulose. There is some speculation, however, that bcsC plays a function that

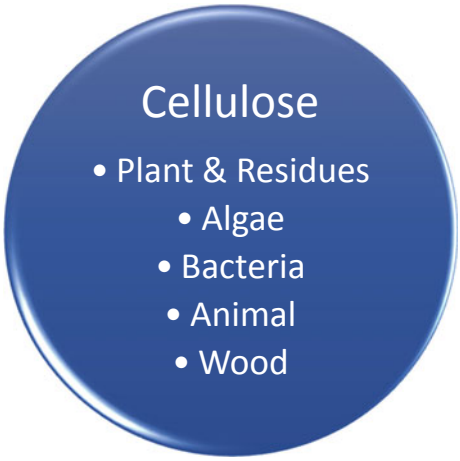

Fig. 1 Occurrence of cellulose in different organisms

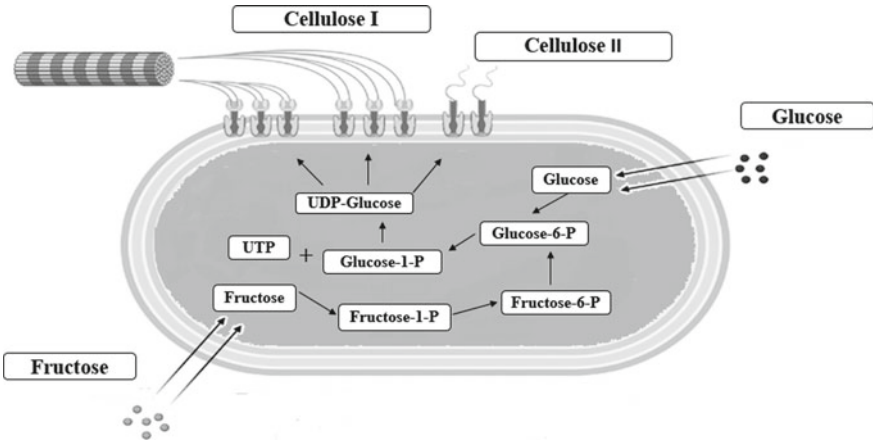

Fig. 2 Biosynthesis of bacterial cellulose I and II from glucose and fructose

is similar to pore-forming proteins in the creation of cell membrane holes and that the proteins it encodes. The functions of bcsD and bcsC are still a mystery. After a successful fermentation, only secondary metabolites, cellulose, microbial biomass, and any nutrients that were present in the growth medium remain in the pellicle. A crystalline cellulose matrix made up entirely of pure cellulose may be easily made by removing all of these impurities. While bacterial cellulose and vegetal cellulose have the same molecular structure, their overall physical and chemical properties are vastly different. Bacteria employ metabolic pathways in a well-ordered fashion to produce cellulose, as shown schematically in Fig. 2.

3 Molecular and Crystal Structure

Natural cellulose is defined by definite intrachain, intersheet, and interchain hydrogen bonds as well as van der Waals interactions between these chains [34]. The alkali treatment of cellulose I results in an irreversible transformation, resulting in the production of cellulose II [23, 43]. Hydrogen bonds between sheets constitute the third class of cellulose structure [115], which is cellulose III. By heating the cellulose I and II back into their original state, it is possible to return it to its original state, which is the reversible synthesis of cellulose III.

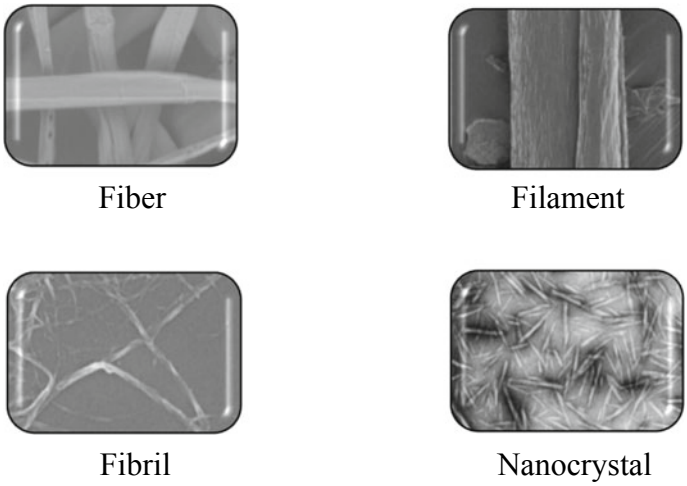

Fig. 3 Different forms of cellulosic particles. The molecule may assume different shapes and forms depending upon functions and uses in organisms and secretory product. These forms can be modified accordingly for biomedical uses

4 Cellulosic Particles Have Various Morphological Forms

Fibers, crystals, filaments, and micro/nanofibrils of cellulose are all examples of the many ways in which cellulose may be obtained or extracted from a variety of sources (Fig. 3). Each kind of cellulose particle has a particular shape, morphology, aspect ratio, crystallinities, and physiochemical features."

Cellulose I is found in natural celluloses, whereas cellulose II and III are present in synthetic materials [43, 48, 111, 115]. Paper and pulp industry is entirely dedicated to altering and simplifying synthetic cellulose.

5 Cellulose Properties

5.1 Cellulose Solubility

Biological uses are hampered by cellulose's insoluble nature in water and other common solvents. Cellulose molecules are stabilized by electrostatic interactions, as well as hydrophobic and intramolecular hydrogen bonds inside the integrated fibrils, resulting in hard bundles with multiple backbone hydroxyl groups. The total effects of hydrogen bonding on stabilization are not entirely known, although electrostatic and hydrophobic interactions may be significant, according to new study [59]. Water and the bulk of traditional solvents are no longer soluble due to the ensuing tight links

Table 2 Typical elastic modulus, tensile strength, and elongation to rupture of common cellulosic particle types

Cellulosic particle types	Elastic modulus (GPa)	Tensile strength (MPa)	Elongation to rupture (%)
Plant fiber	5–130	300–1050	1–8
Wood pulp fiber	14–40	380–1240	3–22
Wood CNF	14–84	1000–1300	4–8
BC	60–115	–	–
Tunicate cellulose	110–200	–	–
CNC	60–220	7500–7700	–

between the interwoven cellulose strands. Designing energy-efficient systems for the dissolution of cellulose necessitates using sophisticated solvents. Ionic liquids may dissolve cellulose and are considered environmentally acceptable solutions.

Dissolving cellulosic materials employing ionic liquids has both advantages and disadvantages, including high energy consumption and high prices as well as solvent recovery also not properly done due to difficulty [130]. The dissolution of cellulose has also been tried in organic solvent N-methyl morpholine-N-oxide monohydrate (NMMO·H2O). After being dissolved, NMMO is a safe solvent that may be recycled in over 95% of situations [129] (Table 2).

5.2 Mechanical Properties of Cellulose

Cellulose-based biomaterials having polymers and inorganic material have been focused for high-performance mechanical and functional materials. The properly made crystals of cellulose-I have great tensile strength which could be helpful in biomedical applications. Cellulosic nanofibers possess extraordinary mechanical qualities like high specific strength and modulus), intermolecular attractions including weak hydrogen bonding in cellulosic chains, and crystalline structure. The crystalline elastic modulus of cellulose I ranges from 124 to 155 GPa [108, 110, 127].

Highly polymerized cellulosic nanoparticles moduli of crystalline nature are important for medical use [76, 124]. Its extraordinary mechanical properties resemble soft tissue [40]. Biocellulose acquires some striking mechanical properties after drying. The elastic modulus of cellulose, depending on the source, ranges from 60 to 115 GPa [32]. The mechanical properties of BC show that it can interact with flexible, smooth muscle cells, and nanofibril structure is comparable with collagen networks.

5.3 Cellulose Hygroscopic Properties

The exceptional mechanical properties, cellulose's poor misty strength is a major drawback in many applications [74]. Water-forming hydrogen bonds develop naturally in cellulose, making it hygroscopic. Water molecules are attracted to and held in place in the cellulose framework. Cellulose fibers are only partially permeable to water because of their disorganized nature. It follows that disordered domains and the fiber saturation threshold have a 30 percent association. Cellulose and composite materials and cellulose-based hybrid may be processed in an aqueous medium because of the cellulose's water swelling property. However, the embedded hydrophilic polymers and hydrophilic surface of cellulose, as well as wet air adsorption on the hydrophilic surface of the material, make these goods susceptible to significant swelling. Nanocellulose-based materials have a larger surface area than fiber-based materials, which means they are more likely to absorb water and swell. When chemically modified to carry charged groups, cellulose-based materials that have undergone chemical alteration provide an osmotic swelling pressure that enhances water absorption [117]. Cellulose's hygroscopic properties may prevent it from being used in a certain biological application.

5.4 Toxicity

Focusing on biological applications, material toxicity is a big issue. Despite the fact that cellulose particles are derived from non- or low-toxic sources, their cytotoxicity and biocompatibility may be altered by a variety of factors, including particle size, surface modification, hydrophilization, hydrophobization, and the aggregation of the particle. Harmful materials made comprised of nanoparticles are often thought to be more toxic due to their small particle size [79]. Cellulose nanoparticles cytotoxicity, genotoxicity, and immunotoxicity, contradicting in vitro evidence, have been reported. When cellulose nanoparticles come into touch with the body, a common biological response is inflammation. It is possible that it will go away on its own. Cell toxicity in acute testing has been attempted to be linked to (of a specific kind and chemical function) cellulose nanoparticle size and stiffness, but no definitive relationship has been discovered. The long-lasting effects of cellulose nanoparticles on living organisms must thus be studied in more depth, since these results may vary from those of acute and in vitro studies.

5.5 *Regeneration and Molding of Cellulose into Various Morphologies*

Selectively dissolving ligno-cellulosic fibers using solvent LiCl/DMAc have been established to manufacture all-cellulose composites. The modification in surface layer of the cellulose fibers is made by partially dissolving the composite preparation to make matrix, as difference to melting of fiber through selective melting process as in case of all-PP composites [105].

Aerocelluloses are an exceptional family of cellulosic materials having large porous solid surfaces with networks of fibrils which has low density, high porosity, and excellent surface area, to make cellulose aerogels. Aerocelluloses are created without major changes in its network shape, with the help of a number of processes like cellulose breakdown, drying with supercritical CO_2, solvent exchange and gelation [85].

The desired material can be produced with properties outstanding to specific use, a series of combination materials has been widely used accordingly. The present interest is growing to make cellulose bio-based products and modify it through biological innovation technologies which can modify cellulose as ecofriendly material and decrease use of fossil fuels [24, 84].

6 Use of Cellulose and Its Derivatives in Pharmaceutical Industry

6.1 *Applications in Medication Delivery Systems*

Mucoadhesives and bioadhesives are drug-containing polymeric films when combined with moisture or mucus components are capable of adhering to biological membranes. Bioadhesives, a new idea in medication delivery, were developed in the 1980s. Potential approaches for prolonging the duration and on various biological membranes increasing the localization of drug delivery systems have been identified in recent years [30, 77].

These dosage forms are easier for patients to swallow because of their tiny size and thinness. It is also possible that these new drug delivery systems may enable controlled release drug formulations to supply dosages less often since the medicine will linger at the absorption site for a longer time period. Drug content interaction with the mucosal barrier and enhanced transport of drugs via a patient's mucous membranes may also be enhanced by these dose forms, mainly in the case of treatments that are not well-absorbed [69],). The constrictive intercellular connections-specific polymers may be used in these formulations, hence altering epithelial permeability. Orally sticky versions of sensitive drugs may benefit from some of these polymers by suppressing proteolytic enzymes [57].

The cutting-edge medicine delivery technology, bioadhesives are considered rectum, vagina, ear, nose, and gastrointestinal system may be treated with these dose types. Film-forming polymer and glue are the principal excipients in these mixtures. Adhesive polymers that may stick to mucosal or skin surfaces include synthetic, semi-synthetic, and natural macromolecules. The bioadhesive polymers as broad range of polymers have been used. Carbopol, polycarbophil, and acrylic derivatives as well as natural polymers like carrageenan, pectin, and acacia as well as in bioadhesive formulations semi-synthetic polymers like chitosan and cellulose are used [22]. A common component of bioadhesives is cellulose ethers, which are cellulose derivatives. Many formulations, such as ophthalmic, buccal, nasal, and vaginal transdermal formulations, may be used using these polymers alone or in combination. Cellulose-ether derivatives including ethylcellulose (EC), hydroxyethylcellulose (HPC), carboxymethylcellulose (CMC), and hydroxylpropylmethyl cellulose (HPMC), as well as anionic ethers like sodium carboxymethylcellulose (SCC), have been employed in bioadhesives more recently (NaCMC). Both the polymer's capacity to absorb water from mucus and the pH of the target location have a significant effect on polymers' adhesive capabilities. Since certain bioadhesive polymers, such as polyacrylates, have dramatically variable sticking properties at varying pH levels, the kind of bioadhesive preparation should influence the choice of adhesive polymer. Bioadhesives polymers such as NaCMC and HPC are less sensitive to the pH of the medium when it comes to adhesion time and adhesion force [30].

Bioadhesives for oral, buccal, ophthalmic, vaginal, and transdermal use have all been tested using in combination with other polymers or in cellulose ethers alone [89, 113]. The adhesion qualities of cellulose ethers, for example, adhesion force and adhesion time, may be improved by combining them with other sticky polymer or polysaccharide groups hydroxypropyl beta-cyclodextrin, polyvinyl pyrrolidone (PVP), pectin, dextran, polycarbophil, carbopol(s), and mannitol have all been shown to work well with HEC, HPMC, or Na CMC in the literature [46].

6.2 Application in Pharmaceutical Coating Techniques

Pharmaceutical companies frequently coat solid dosage forms like pellets and tablets to prevent absorption of the active ingredient into the body. This is done for a variety of reasons. For example, they may prevent the breakdown of acidic or enzymatic medications by protecting them from humidity and oxygen, masking odors or tastes, and creating time- or site-specific release characteristics (Barzegar jalali et al. 2007; Gafourian et al. 2007). Cellulose ester and ether derivatives are often used to coat pharmaceutical substances. Most cellulose ethers are hydrophilic and create hydrogels when they come into contact with water, making them hydrophilic. Hydroxypropylmethyl, methyl, and hydroxypropyl celluloses are all water soluble, but only ethyl cellulose isn't. There are many other cellulose ethers as well. Cellulose ethers, whether soluble or insoluble, have the potential to absorb water and solidify on contact with it. This coated dosage form gets dissolved into hyrogels when put in

water while the insoluble cellulose ether coating remains a gel around the tablet, allowing drug molecules to diffuse out of the tablet and out of the gel. There are two types of dosage forms that fall under this category: diffusion-controlled and dissolution-controlled. Cellulose esters in certain pH ranges are often either water insoluble or water soluble. When exposed to water, materials like CA, CAB, and CAP do not gel and are widely used to build semipermeable, pH-sensitive microporous membranes that are semipermeable to water. A broad variety of drugs may be covered by these membranes, which are often employed in enteric or osmotic drug delivery systems. It may be utilized to make various cellulose membrane filters that are often used in pharmaceutic manufacturing.

6.3 Application in Solid Dosage Formulations with Extended Release (ER)

6.3.1 Coated Extended-Release Formulas

Pharmaceuticals extended release are dose forms that allow for a greater or twofold decrease in the medicine administration frequency compared to regular dosage forms. Matrix or coated formulations are also viable options for creating these compounds. To make coated ER formulations, polymeric film coatings with or without the ability to form gels are often utilized. Coated ERs have a diffusion-based drug release mechanism, while matrix-based ERs have a matrix-based release mechanism. Cellulose acetate is by far the most often used cellulosic polymer. Some organic solvents, such as toluene, ethanol, and chloroform, are soluble in ethanol cellulose; however water, glycerin, and propylene glycol are not. The aqueous dispersions of Surelease® Aquacoat® or (Colorcon) (FMC BioPolymer) or their organic solutions may be cast-off to coat compositions with extended release. After consuming these formulations, a viscose gel forms around the tablet, making it impossible for the medication to be released from the dosage form easily. To reach the bulk dissolving medium, drug molecules must diffuse through this barrier, which results in a longer release time than with the equivalent uncoated conventional formulation. The air-suspension coater or fluidized bed equipment may coat tiny types of solid pharmaceuticals such as pills, beads, or granules.

6.3.2 Extended Release Polymeric Matrices

Using matrices to control the release of medications from dosage forms is a simple but very successful approach. It is possible to create these systems more rapidly and without the need of costly equipment. In most cases, the drug, polymers, and filler are simply mixed together and then compacted in a two-stage or single process. Polymeric matrices would be used as drug delivery strategies to create modified release

dosage forms. Molecularly or as microscopic particles, the drug is dispersed across a polymeric network in these devices. (Roy et al. 2002) Non-erodible and non-erodible drug delivery matrix was the most common types of matrices. Hydrophilic matrices are used to control the medicine release rate from solid dosage forms has become a standard practice because of its process and economic development advantages [18]. Tablets with controlled release matrixes made from hydrophilic swell-able polymers have been prominent in the last two decades of drug development. Since hydrophilic matrices may be made using various rate-controlling polymers such as cellulose derivatives, and in particular, their derivatives, they are the most commonly referenced in pharmaceutical literature and commercially available oral-controlled release matrices. They may be compressed directly into matrices because to their excellent compressibility.

6.4 Application of Osmotic Medication Delivery Systems

There has been a lot of buzzes lately about developing new ways to distribute medicines (NDDS). (CR) Controlled release oral systems have the largest share of the NDDS market due to its advantages over competitors. In the vast majority of oral CR systems, a matrix, reservoir, and osmotic device are used. (Shokri et al. 2008a) Osmotic devices are considered innovative among the numerous types of CR systems. As a power source and a driver for medicine delivery, these formulations rely on osmotic pressure. Traditional CR systems (matrices and reservoirs) may be influenced by physiological characteristics such as presence of gastrointestinal motility, pH, and food; however, drug release via oral osmotic systems is usually unaffected by these conditions. Using a laser or mechanical drills, a tiny hole is drilled into the semipermeable membrane (SPM) that surrounds an osmotically active core. The real gadget is a coated tablet with a medicine delivery port in the middle of the opening (Fig. 4) via elementary osmotic pumps (EOPs).

6.4.1 Osmotic System Formulation in Semipermeable Membrane

Two essential components are required for any osmotic delivery system: a semipermeable membrane and an osmotic core (SPM). Every kinds of osmotic drug delivery systems, cellulose acetate are the principal polymer utilized to create SPM (CA). The most important cellulose ester derivative, for usage in osmotic systems, this polymer has excellent mechanical characteristics. CA is water insoluble in both alkaline and acidic conditions. Only tiny molecules, like water, may flow through the CA coatings; bigger molecules, such chemical medicines, cannot. For a more flexible SPM membrane, plasticizers are employed in the formulation. (Shokri et al. 2008a, 2008b) In the formulation of osmotic pharmaceuticals, few examples of plasticizers used, PEGs (polyethylene glycols), castor oil, sorbitol, propylene glycol, triacetin, ethylene glycol monoacetate, diethyl phthalate, dimethyl phosphate, and diethyl tartrate;

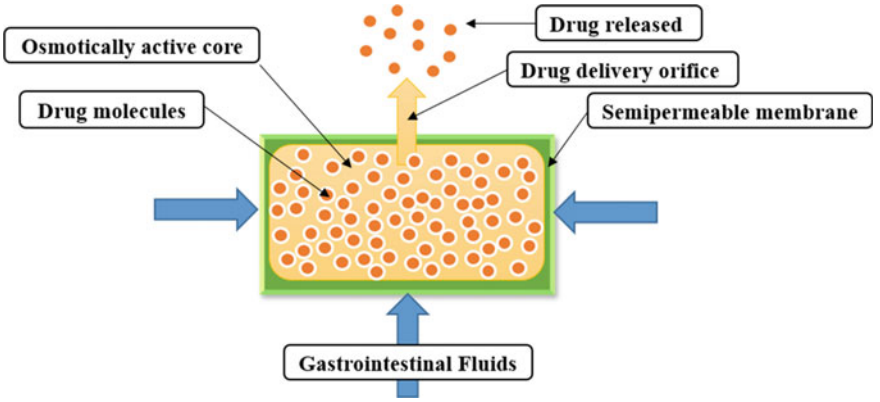

Fig. 4 Elementary osmotic pumps (EOPs) system

[82, 90] (Makhija and Vavia 2003; Liu et al. 2000a, 2000b). Plasticizers with both hydrophilic and to achieve the desired medication release properties hydrophobic qualities are often used. In order to use CPOPs, you will also need pore formers and other similar add-ons. For pore formation, with a high water solubility, hydrophilic polymers are best. In these devices' SPM water-soluble cellulose, ether derivatives may be used as pore formers. Low molecular weight grades of these polymers are appropriate because of their faster dissolving and reduced viscosity. In CPOP formulations, low molecular weight HPMCs and MCs have been used as pore-forming agents. A suitable liquid base is used to dissolve or disperse SPM components such plasticizers, film formers (CA), and pore formers, before they are applied to central cores.

When dissolving cellulose acetate in a coating liquid, solvent solutions including acetone/ethanol are often used [81]. In other studies, cellulose acetate has been used to cover osmotic cores by dispersing small particles in an aqueous solution. They are, nevertheless, less permeable than CA membranes. For osmotic devices, the SPM has also been used using ethylcellulose and ethylhydroxylpropyl cellulose such as HPMC. According to [39, 120], and [72], "hydrophilic cellulose ether derivatives have been included in these formulations to improve SPM permeability.

6.4.2 Central Core Osmotic Systems

The osmotic pump heart is commonly a simple crushed tablet. Additionally, this tablet comprises compressibility enhancer, filler, lubricant, and free-flowing agent, as well as the active drug(s), hydrophilic polymer(s), and an osmotically active agent(s). However, before being combined with other ingredients in 2 or three-layered (Sandwich systems) cores, in one or two separate layers, polymers were compressed on one or both sides of the drug layer and compressed into tablets for one compartment

devices, while this was not the case in polymer-only devices (controlled porosity OP and EOPs) [53]. Water absorption and expansion capabilities are expected for these polymers. Osmotic device core formulations are based mostly on cellulose derivatives. Water-soluble cellulose ethers, as core polymers, are often used because of their hydrophilicity and excellent swelling properties. A wide range of polymers with varied molecular weights are currently most often used for this purpose. A large osmotic pressure differential between the device's outside and inside causes water to enter the system following exposure to water. This water is absorbed by the polymer(s), causing them to expand. The swelled core polymer(s) is what causes the drug solution to eject out the drug release aperture at a consistent pace [90].

6.4.3 Application in Solid Dose Form with Enteric Coating

The colon and small intestine solid dosage forms of enteric coated are designed to release their drug(s) particles in the lower gastrointestinal tract. Enteric dose forms are a kind of oral medicine that begins to release its active ingredient after passing through the stomach. The formulation of pharmaceuticals formed by enteric oral dosage is suited that may irritate the inner gut layer of protection, such as nonsteroidal anti-inflammatory medicines (NSAIDs). pH-dependent carboxylic acid groups are often used in formulations for enteric coatings [60]. These polymers during digestion are non-ionized and ionize as the pH rises toward a moderate alkaline zone, which is similar to the situation in the small intestine. These polymers must also be able to create robust films in order to provide coatings with high integrity that are uniform.

6.4.4 Application as Agents that Increase Compressibility

The medicines in dosage forms used or accessible to humans are in the form of tablets. Tablets widespread acceptance may be attributed mostly to the advantages they provide over more traditional forms of medicinal delivery. Additionally, they are easier to administer and are more stable than liquid or semisolid doses. Tablets may be made using compression and molding, two common methods. Compression is the most common method for making tablets. The quickest compression method to make a tablet is the most straightforward and direct compression, in which the medication and any excipients are compressed and mixed together in a single step with the required compression force. Medium- to high-potency pharmaceuticals in tableting, when the drug content is lesser than 30% of the formulation, this method is typically utilized. In further cases, less compactable medications are in a higher concentrations; tablets are manufactured using either dry or wet granulation techniques. Materials go through a series of compression steps in the dry granulation process to improve

their compressibility. Powder mixtures are first crushed using slugging and roller compaction techniques before they are finally tableted out for use.

It is common for the drug content to be difficult to compress, especially if the formulation contains more than 30 percent of the total drug content. Compressibility enhancers are useful in these cases because they make it easier to make a good tablet with features that are well-known in the pharmaceutical business. It is true that all cellulose-based polymers may be compacted, but microcrystalline cellulose in particular has excellent compatibility. In tablet manufacturing, these grades are commonly used as compressibility enhancers since they may significantly boost the compressibility of low-compactable powder mixtures. Classes of MCC differ fundamentally in its form, size of particles, surface area, porosity, and density.

6.4.5 Application as Gelling Agents

When a gelling agent is added to an aqueous liquid media, it creates a semisolid solution with a jelly-like consistency made up of tiny particles or large molecules. Recent years have seen an increase in the use of synthesized and semi-synthesized macromolecules in pharmaceutical dosage forms as gelling agents. Ingredients like natural gums and carbomers are included in this category. CMC and HPMC in pharmaceutical applications are two of the most often used gelling agents. Except naturally occurring gelling agents, they are less vulnerable to microbial contamination such as sodium alginate, acacia, gelatin, pectin, and agar. Their jellification processes are thermal, only MC grades dissolve more quickly. After physically combining the polymer granules in cold water, the dispersion is heated to a temperature of 60 to 80 degrees Celsius and then allowed to cool to room temperature in order to (except MC grades) form a gel product. Single-phase gels are a byproduct of these polymers. Low concentrations of electrolytes increase gel viscosity via the salting-out process, but high concentrations (more than 3–4 percent) may precipitate polymer and cause structural problems in the gel. The gels of these polymers are most stable and clear when the pH is between 7–9, whereas acidic pHs may cause them to precipitate out of the gel system. According to the type and molecular weight, cellulose derivatives have different minimum gel-forming concentrations, although the intermediate range w/v' s is between 4–6 percent [109]. In medical gels, these kinds of cellulose derivatives employed may have a significant impact on the release of drugs from gel compositions [35]. Additionally, these gels may be used as a basis for cutting-edge drug delivery systems like liposomal formulations.

6.4.6 Applications as the Use of Stabilizing and Thickening Chemicals

Cellulose derivatives are often used to thicken emulsions and suspensions in the pharmaceutical industry. These polymers may also increase the organic coating solutions

viscosity and other non-aqueous pharmaceutical solutions. One of the many advantages of viscosity-enhanced medication solutions is improved feeding control and a longer drug residence time in topical and mucosal formulations [31]. Some drugs in oral dosage forms, such as insulin, that are difficult to absorb have been demonstrated to benefit from viscosity enhancement on rare occasions. Cellulose ethers are used as thickeners or viscosity builders at lower concentrations than required to produce gel. Pharmaceutical dispersion systems rely on these polymers to be stable, especially in coarse emulsions and suspensions. After product shaking, the stock equation predicts that increasing the suspension's viscosity will reduce the sedimentation rate of the dispersant and enhance dispersion uniformity. Improved mechanical and thermal shock resistance may be achieved by using these polymers. Especially, those with higher molecular weights, for example, cellulose ethers, are ideal pharmaceutical dispersion systems for increasing stabilizing and viscosity liquid as suspensions and emulsions. The molecular weight of cellulose ether solutions is directly proportional to their viscosity.

6.4.7 Application in Solid Dose Formulations as Fillers

Cellulose and other polymers are often used as fillers in tablet and pill dosage forms. Cellulose excipients have long been appreciated for their versatility in pharmaceutical formulations, making them ideal for use in the production of solid dosage forms, when used as a filler in solid pharmaceuticals cellulose and its derivatives offer many advantages, including pharmacological inertness, indigestibility by human gastrointestinal enzymes, and compatibility with most other excipients. The esophageal and gastric mucosa are protected by these polymers; thus irritation is not a concern. Cellulose-ether derivative and pure cellulose fillers may be used in these products.

6.4.8 Application as Binders

Binders are crucial components of solid medicine formulations created by wet granulation. Medicinal material is blended with other excipients, treated with an organic or aqueous solvent, and then dried and milled into granules using the wet granulation process. Binding qualities of the cellulose and its derivatives are useful in the wet granulation process. Including PH-101, as binders, wet granulation uses a variety of MCC grades. Other cellulose derivatives, such as HPC, MC, and HPMC show high binding properties in wet granulation. When making wet granules, low substituted HPC (L-HPC) is also used as a binder [21, 119]. Despite their lower water solubility than regular grades, low substituted cellulose ethers are good binding agents. Cross-linked cellulose derivatives and cross-linked cellulose (CLC), such as cross-linked NaCMC, in pharmaceuticals may also be used as excellent binders.

6.4.9 Applications as Deteriorating Substances

Oral solid dose forms, such as tablets, undergo a series of procedures before they may be absorbed into the body. The first step is disintegration in the breakdown of an oral dosage form in an aqueous environment after administration. Widen the surface area for drug release from dosage forms may be achieved by reducing solid dosage forms into small bits. The first known disintegrant is starch. As early as 1906, it was known that potato starch or maize starch was responsible for the disintegration of tablet formulations. Pre-gelatinized starch was created as a disintegrant since starch is not particularly compressible. Traditional disintegrants include MCC and pre-gelatinized starch. Disintegrants that are more than a decade old, referred to as "super disintegrants," have begun to supplant earlier disintegrants. At lower quantities than starch, super disintegrants may operate and do not impair the formulations' elasticity. Crospovidone (Polyplasdone XL, Kollidon CL), sodium starch glycolate (Primogel®, Explotab®), and (Nymcel and Ac-Di-SolTM) cross-linked sodium carboxymethyl cellulose, in wet granulation process with a 2–4 percent effective concentration, are the three main groups of these cross-linked polyvinyl pyrrolidones. High disintegrant efficiency speed up the dissolution of medicines in aqueous solutions by modified cellulose compounds [14].

6.4.10 Application as Flavor-Mapping Substances

The medication's bitter taste is by far the most prevalent and most objectionable flavor. Disgusting dosage forms reduce the likelihood that patients will take oral medication formulations. The taste receptors on the tongue are sensitive to a wide range of flavors. Onion-shaped structures called taste buds contain between 50 and 100 taste cells. Saliva breaks down chemicals found in food and drugs, allowing them to enter the body via the taste hole. They either interact with ion channels or taste receptors on the surface of the cell. Taste cells undergo electrical changes as a consequence of these interactions, which contribute to the delivery of chemical signals to the brain and subsequent neurotransmission. Sour and salt responses are ion channel types, whereas bitter and sweet reactions are surface protein responses [21].

When formulating oral dose forms for drugs with big dosages or unpleasant tastes, it is critical to consider flavor masking. It is especially important to improve the flavor of liquid dose forms since they trigger taste receptors more rapidly and more intensely than solid dosage forms. By coating them, micro-coating taste may be hidden in solid dosage forms (in the case of microscopic microcapsule, powders, or granules) or (in the case of tablets, pellets, or pills). Using these coatings, the medicine may be kept from coming into contact with the patient's taste buds, but the drug compositions will not be affected in any way. Soluble cellulose ether derivatives are suitable for this use.

7 Applications of Cellulose in Biomedicine

The applications of cellulose with live tissue where the material needs to remain in touch and should not produce any cytotoxic or other adverse effects, for biomedical applications evaluating the confirming their interaction with cells and biocompatibility of materials, are a crucial necessity. When compared to synthetic biopolymers, cellulose has the distinct advantages of biodegradability, biocompatibility, cheap manufacturing costs, abundance, renewable resources, nontoxicity, and superior mechanical qualities. Due to their special capacity ranging from months to a few years, to be completely resorbed in pre-designed time frames, bioresorbable polymers with these characteristics have the potential to play a highly significant role in biomedical applications.

7.1 Wound and Skin Dressings

The adjustable excellent biocompatibility, mechanical qualities, adaptable and drug release capabilities, customizable surface structure and chemistry, and moisture maintenance of cellulose biomaterials have generated significant interest in their use for artificial wound and skin dressings. As a result, a variety of fake skin products are offered in stores. The skin, which has three separate layers (dermis, epidermis, and hypodermis), in the human body is the biggest organ. The epidermis, the outermost layer of skin, plays a crucial part in shielding the body's internal environment from the outside world and avoiding contamination and infection by dangerous organisms. The nerves, sweat glands, blood vessels, and hair follicles are situated in the dermis, the skin's middle layer. The hypodermis, the skin's lowest layer, is where fat is found [94].

Nanofibrillar cellulose has also been mentioned. Functionalized nanofibrillar cellulose dressings have been utilized to promote skin regeneration and healing for burn sufferers. The nanocellulose dressings' mechanical and physical characteristics may be tailored to the patient's need. Functionalized cellulose dressings have been shown by Hakkarainen et al. to be better to currently on the market goods like Suprathel®. No inflammatory reaction to the cellulose dressing and epithelialized skin regeneration was seen. The dressing easily adheres to the wound, but after skin regeneration is complete, it naturally separates. Despite the dressing's lack of antibacterial properties, it did not encourage bacterial growth. Bacterial nanocellulose has been used on full-thickness skin defect models and is biocompatible. Utilizing these porous membranes promotes a decrease in inflammation and a speedier healing process.

The thickness of the membrane can affect the pore size during the manufacture of the cellulose components. For instance, the structure of BC films' bottom side is rougher and looser than its top side. As cell diffusion and migration were more permitted, it has been notify that when compared to control gauze and the more dense

top side the enhanced porosity boosted the wound healing rate and decreased the inflammatory response [58]. Infection and water loss were more effectively stopped by the top side's reduced porosity. Hydrogels made of cellulose Nano-whisker and polyvinyl alcohol (PVA) have also been used in applications for wound healing. Including nano-whiskers gives the hydrogels' physical characteristics more control. In particular, the porosity may be adjusted; while the cellulose nano-whiskers reduce pore size, they have no impact on the gel-forming process. The composite materials are mechanically strengthened by the addition of cellulose nano-whiskers. The presence of nano-whiskers in the context of the skin application did not cause the drying rate to increase over the in vivo ideal range. Additionally, against bacterial invasion, the composite materials provide defense.

7.2 Applications in Bone Marrow

Cellulosic biomaterials may be modified to work in the mechanically and rigid demanding environment of bone. Building biomimetic constructions using the biomaterial structure as a template is a viable strategy, as was covered in the section on skin and wound healing. It has been demonstrated that gyroidal cellulose scaffolds may be produced using a reverse templating approach in the setting of bone (Torres-Rendon et al. 2015). With this strategy, researchers can specify and regulate pore geometries mathematically. This study emphasizes that because macroscopic features are determined by nanoscale details, bottom-up techniques for building 3D scaffolds are essential.

In contrast to templating, electrospinning is a preferred technique for making nanocomposites for bone tissue substitutes. Because hydrogels' mechanical qualities are insufficient to sustain the physical stress placed on bones, nanocellulose is frequently added to them. In the case of electrospun matrices of polylactic acid (PLA) and polyvinyl alcohol (PVA) hydrogels, cellulose nanocrystals can serve as physical supports [128]. Using techniques like maleic anhydride grafting, PEG grafting, and sodium dodecyl sulfate (SDS), the surface chemistry may be altered to increase the tensile strength and interfacial adhesion between the cellulose and PLA. Additionally, the matrix fibers' diameter and polydispersity are decreased by the nanocrystals. The inclusion of cellulose nanocrystals improves the mechanical and thermal stability. These scaffolds are biocompatible and have a tensile strength more than 10 MPa. Different weight ratios of electrospun nanofibers can be employed to create bio-inspired bone formations.

The high porosity of natural bone has made approaches for producing extremely porous biomimetic materials that are essential for bone tissue engineering. Laser ablation of cellulose acetate electrospun fibers is one method of creating pores. Without influencing the surrounding material, pores of diameters ranging from 50

to 300 m may be created. These structures can undergo further nanoscale processing to mineralize to a degree that is comparable to levels of hydroxyapatite in living tissue. The porous mineralized scaffolds boost osteoblast adhesion and cell density at the pore locations. Natural bone is mostly made up of collagen and minerals with hydroxyapatite-like chemical makeup. The ability to mimic this intricate structure is crucial for bone tissue creation.

7.3 Applications in Neuron

The adaptable surface mechanical/physical characteristics and chemistry of cellulose scaffolds have made it a good material for differentiation and 3D nerve cell growth. Enhancing integrin-based attachment and cell—scaffold interactions can be achieved by chemical modification and protein coating of cellulose materials. Electrical stimulation is a problem in nerve tissue engineering that is specific to a subset of cell types, such as neurons and myocytes. As a result, 3D nanostructured, electroactive biomaterials are needed. Cellulose scaffolds covered with conductive substances like (PEDOT) poly-(3,4-ethylenedioxythiophene) and multi-walled carbon nanotubes, or carbonization can be employed to meet these requirements. Such materials are biocompatible and promote neural differentiation in addition to having tunable mechanical properties, electrical conductivities, and pore sizes.

Psychiatry's pharmacological loading is crucial, in addition to growth factor loading. Drug delivery through the use of cellulose-based biomaterials is a potential approach. Cellulose is a prime contender for nerve tissue healing and drug delivery systems due to its outstanding biocompatibility, extremely porous structure, customizable stability, and programmable mechanical characteristics. The use of cellulose constructions as nerve guiding conduits for rat sciatic nerve deficits has been demonstrated to be significant. The findings of this investigation demonstrated that cellulose materials containing citalopram can modulate the sciatic nerve's functional recovery.

7.4 Blood Vessels

The two most commonly used vascular graft materials are expanded poly-(ethylene terephthalate) (PET) and polytetrafluoroethylene (ePTFE). Despite the high success rate of these materials, their applicability to small vessels is limited due to thrombosis. As a result, materials that are compatible with blood and have the right biochemical and physical characteristics are required for vascular engineering. Bacterial cellulose structures show no discernible difference in platelet consumption and coagulation

when compared to commonly utilized graft materials, such as ePTFE, PET, and heparin-coated PVC. However, it should be noted that for both 4 and 6-mm-diameter tubes, BC had complement activation values sC5b-9 and sC3a that were much greater than those for the other materials. Furthermore, an in vivo study employing hamsters showed the materials' great biocompatibility and minimal immunological response. A bacterial blood channel implanted in sheep carotid arteries in vivo demonstrated epithelial cell coverage and patency for up to 13 months. However, there were discrepancies in the patency of the unmodified structures employed in this investigation. Contrarily, bacterial cellulose blood arteries produced with the use of oxygen-permeable polydimethylsiloxane (PDMS) templates have excellent mechanical qualities. Endothelialization was seen after these veins were successfully inserted into rabbit femoral arteries [128].

7.5 Drug Delivery

The release of medications at the right moment, in the right amount, to exactly targeted organs is referred to as a drug delivery system. Drug delivery systems distribute medications to the targeted organs, tissues, or cells. The transfer method may be adjusted to react to environmental cues including light, magnetic, chemical reactions, temperature, pH, and electric fields. In the pharmaceutical sector, cellulose has a long history of usage as a tablet covering when combined with different excipients for oral delivery. Even though cellulose and its derivatives have a long history of usage in tableting, research is still being done on their potential application in cutting-edge drug-loaded systems in terms of the rate of tablet dissolving as suitable excipients or extended drug release as innovative drug carriers [125]. Cellulosic materials should encourage tunable diffusive characteristics and dissolvability as a medication delivery mechanism. For instance, it has been noted that the drug distribution patterns of cellulose and its derivatives in oral dosage forms might be instantaneous, regulated, or delayed [29]. Additionally, since cellulosic materials naturally withstand the stomach's acidic environment, it is particularly practical to utilize them as enteric coatings on capsules or tablets.

The high beneficial qualities, such as high shear strength and high affinity with other substances, shear modulus, regenerative properties, biocompatibility, suitable flexural, biodegradability, and tensile strength, CA nanofiber mats, have been used primarily in a variety of pharmaceutical applications. Particularly, the development of topical and transdermal drug delivery methods has given CA-based drug-loaded nanofibers a great deal of attention [126]. Additionally, cellulose acetate phthalate is a cutting-edge substance that offers the best method for pH-controlled medication release. Microencapsulation, which is used in an aqueous or organic media, is one of the crucial uses of cellulose acetate phthalate. Electro spun fibers made of cellulose acetate and phthalate help people avoid HIV infections. Even after dissolving, these fibers pose little threat to vaginal lactobacilli or epithelial cells. These fibers can be

used to load guard against HIV transmission and anti-HIV medications during sexual activity [41]. Typically, extrusion, spray-drying, and coacervation phase separation have been used to do microencapsulation using cellulose acetate phthalate [118].

8 Applications for Cellulose Nanofibers in Medicine and Pharmaceuticals

Cellulose nanowires as a novel compounds involve many factors [49]. The microstructural and chemical characteristics of particulate nanofibers have been examined in this study, and they have been contrasted with those of the widely used tried to capture substance, cellulose fiber. Adsorbent and cellulose nanofibers have different physicochemical characteristics despite sharing almost identical chemical structures. The unique spray-dried nanofibers have undergone evaluations for their rheological properties, humidity levels, and other density variables. In addition, a tablet composition was created utilizing the foot pressure and palletization techniques to test the tensile strength of cellulose nanofibers alone and in conjunction with cellulose fibers. Because cotton nanofibers grains demonstrated the capacity to resist deformations as well as less bendable features, study found that cellulose structure in terms matrix tablets is possible by both maceration and direct compression. In contrast to wet granulation formulation, which did not exhibit any discernible change, dry granulation tablets made with nanofibers patterns of international drug release (95% of the drug after 5 m).

Cellulose nanocrystals, as stiffness modifier, also play a crucial part in product stabilization. Naproxen and celebrex are weakly water-soluble medicines, hence biopolymer-based oil-in-water emulsified formulation were designed for prolonged drug distribution. In order to stabilize the oil/water boundaries of the nanoemulsion in the continuous aqueous environment, class II hydrophobin peptide (Trichoderma reesei) was used as an emulsifiers in this study. Next, to determine the robustness of the microemulsion and envelop serum oil droplets in the celluloid structure in terms fiber network, cotton nanomaterials were also added as a stiffness enhancer. For this reason, the native nanofibers and potential of oxidized has been assessed. The approach ensures for prolonged release of drugs contains 0.15 percent of oxidized nanofibers, according to the results. Similar to this, ibuprofen and naproxen showed fast drug release when coupled with native nanocellulose and important properties proteins. In comparison to typical surfactants used in pharmacological emulsion preparations, the results show but both native and oxidized cellulose nanostructured grades are effective emulsion stabilizers with low concentrations for extended and direct drug release formulations (Fig. 5).

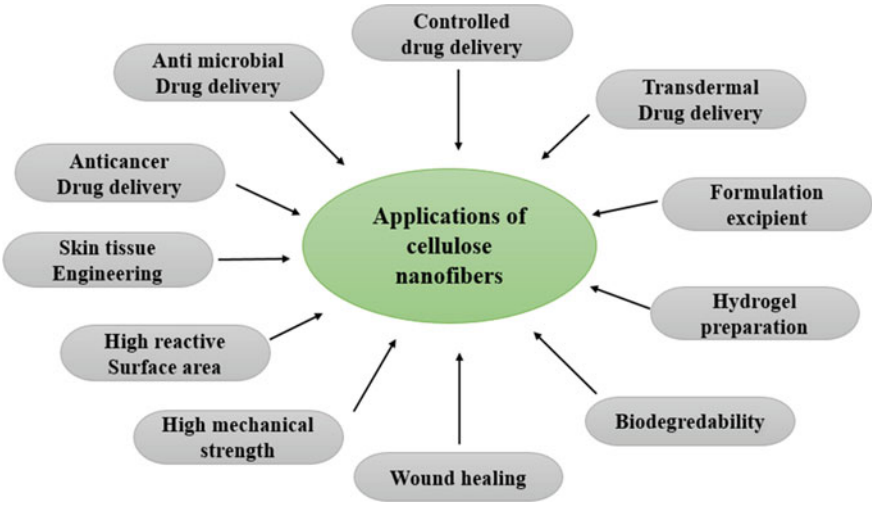

Fig. 5 Application of cellulose nanofibers: The molecule has wide range of application in pure and derived forms

8.1 Applicability in Biomedical Fields

Outstanding characteristics of cellulose fibers, such as a high aspect ratio, population shrinkage, mechanical properties, compressive strength, stability, and biocompatibility, contribute to the development of polymer nanofiber as a suitable alternative for medical synthetic biology, such as capillaries, soft tissue, and the nucleus pulposus. The results of several preclinical tests conducted prior to clinical study have shown that the research into microcrystalline cellulose as blood vessel substitution is both interesting and valuable. Similar to these studies, the number of cases on the use of nanocellulose as soft tissue, cardiorespiratory tissue, and helium atom pulpous suitable alternative bioprinting is still in the beginning phases and primarily focus on comparing the different attributes of lignin nanofibers-based biopolymers with those of actual organs. In addition to offering similar mechanical qualities to the tissue it replaces, the search for polymers to be used for soft tissue substitution should also increase stability, biocompatibility, and life expectancy. Due to the large amount of organic compounds on the surface support, nanofibers also have good enzyme immobilization characteristics.

8.2 Hydrogels Based on Cellulose Nanofibers

The hydrogel polymer was initially developed in the late 1960s and is a family of drug carrier materials for pharmaceutical and biopharmaceutical purposes. It is enhanced with the capacity to retain the hydrophobic core in a 3-dimensional network. A

hydrogel is a homogenous mixture of two (or more) components, with the solid phase being a solid multi-network and the amorphous phase being water [78]. Because they can self-assemble into a variety of structures, such as microgels/microspheres, nanostructured materials, films and membrane proteins, fibers/nanofibers, and microfiber towels, hydrogels are multidimensional materials that can form 2D and 3D networks like spheres, biocompatible, ribbons, and bedspreads [19]. The tensile strength and durability of hydrogels produced chemically from a combination of monomers and bridge are typically low, but hydrophobic nanofibers with charged surfaces have the potential to be implemented as reinforcing agents or even as the foundation of hydrogels. Hydrogels made from microcrystalline cellulose are hygroscopic, compostable, and mechanically robust. Hydrogels made of cellulose nanofibers are widely used in medical applications, drug delivery, biomedical engineering, personal-care products, food additives, and many more biomedical applications [4, 100]. Self-healing hydrogels offer important properties like a less noninvasive injection delivery system to the target spot without gel breakup. Self-healing hydrogels that have excellent tissue adhesion capabilities significantly speed up tissue repair. Additionally, they serve as a vehicle for the transportation of biochemical parameters to the site of injured area, resulting in a localized therapeutic impact. Additionally, the self-healing hydrogels show potential for skin tissue engineering since they might offer an extrinsic matrix-like 3D environment for embedding cells [15]. In a striking study, [54] showed that an injecting technetium-99-m-labeled cotton nanocomposites hydrogel allowed for the research of drug discovery in vivo and the characterization of the localization of the hydrogels.

8.3 Delivery of Antimicrobial Drugs

In the creation of biomaterials, nanofibers provide a permeability spongy network structure. The effective distribution of therapeutic medicines into the wound is made possible by this pore system. Additionally, it functions as a powerful physical barrier against another infection from the outside. However, because cellulose nanofibers lack antibacterial action, they are unable to prevent wound infection. By combining cellulose nanomaterials and antimicrobial compounds via physical or chemical methods, cellulose structure in terms antimicrobial nanomaterials is created. According to the science, silver has undergone the most extensive testing for its ability to fight bacteria and has been used for many years to prevent bacterial contamination [93]. [71] created cellulose nanocomposites and silver nanoparticle-based composite utilizing an electromagnetic assembly process in order to investigate the antibacterial property of silver nanoparticles. Here, nanoparticles and cellulose nanofibers were joined together by complex molecular particles. In a nutshell, cellulose carbon nanotube materials mixed in polymer were bathed in

light silver nanoparticles (methacrylic acid). According to the results, fluorescent silver nanoparticles gave the composites both fluorescence and bacterial properties. With the inclusion of antibacterial agents such chitosan-benzalkonium chloride or chitosan-methylisothiazolinone, cellulose nanofibers-resistant nanocomposite based on sodium alginate was created, as described by [62, 63] in a different work. Under the effect of hydrogen bonding and electrostatic attraction, both bactericidal agents with nano spherical shapes adsorb on the surface of microcrystalline cellulose for a short period of time. [95] studied specifically the antibacterial action of carbon fibers with face derivatization in another unique way. Results revealed that Staph and Klebsiella pneumonia strains were both remarkably resistant to the antibacterial action of polymer nanocomposites made of alkene cellulose nanofibers.

8.4 Medication Distribution via the Skin

For example, a gentamycin-grafted nanocellulose sponge preparation was made by multi-cross-linking nanofibers with cellulose decarboxylation and (3-aminopropyl) triethoxysilane. Cellulose nanocrystals serve as vectors for topical and transdermal drug discovery of antibiotics that cannot be given to people orally. With regard to Escherichia coli and Staphylococcus aureus, the created nanoparticles sponge formulation demonstrated impressive antibacterial efficacy [123]. Hydrogel drug carriers were made using cotton nanofibers obtained from spruce kraft pulp. The findings demonstrated that topical administration of hydrogel to a rat excised wound had appreciable wound health advantages and was effective against Staphylococcus aureus and Escherichia coli. Delivering antimicrobial peptides derived from the bacterium Lactococcus lactis, such as nisin, seems to be another novel strategy for preventing pathogenic bacteria. [122] used electrostatic interaction between the electrostatic interaction of the nanocellulose and the positively charged nisin molecules to introduce peptide nisin into "2,2,6,6-tetramethylpiperidine1-oxyl (TEMPO)"—oxidized smaller the particle size cellulose. Similarly, to free nisin, cotton nanofibrous composites that were poorly absorbed with nisin shown substantial antimicrobial activities against Bacillus subtilis and Staphylococcus aureus. By combining possible probiotics and vascular phytochemicals including alkannin, shikonin, and their analogs, [51] created electrospun cellulose acetate nanocomposites meshes for prospective wound dressings. The outcome revealed that nanofibrous meshes had drug loading entrapment efficiency, ranging from 75 to 96 percent, and suitable dosage forms profiles. As a result, cellulose acetate nanofibrous meshes are transformed into exceptional alkannin, shikonin, and dressings for tissue regeneration.

9 Final Observations

It has been determined that cellulose is a very adaptable substance that may be used to create medically useful materials, such as gels, composites, dental grafts, and dressings for wounds, each of which have unique properties appropriate for their function. These materials offer a workable and affordable substitute to the usage of petroleum-based analogs. As a result of its exceptional physicochemical qualities and nanofibrillar matrix, cellulose is extremely biodegradable. Due to the great degree of natural purity, this substance also shows no toxicity in almost all applications, allowing for the direct use of this dressing. Numerous cellulose biomaterials have been studied for biomedical uses including the creation of wound dressings for moderate- to severe-sized wounds. Despite the dearth of in vivo research, these investigations have revealed the huge potential for these composites to be beneficial in healing wounds. The biophysical and biochemical features must be created from the nanoscale up in order to generate completely functioning tissue. For tissue engineering in the framework of bottom-up techniques, in the area of cellulose-based biomaterials, here, we have distilled a wealth of information. Because of their variety and adaptability of biochemical and biophysical properties, cellulose-based materials obviously have a high capacity to become the next generation of standard biomaterials.

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